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Editorial

Coronary Heart Disease

An Evaluation and Criticism of Present Day Concepts

THE DEFINITION of progress is the replacement of wrong ideas by scientific facts. In the history of medicine this has often involved long and bitter conflict.

Concerning coronary heart disease, there is much to be replaced. The superstructure for this disease, constructed by countless lectures and publications, is not only powerful but it has become sacrosanct. In the beginning this structure was built with good purpose but now it must be reevaluated. The attack on it began when it was shown that surgical operation protected the heart when later on a coronary artery was occluded. The attack began with facts derived from the research laboratory over the past 25 years. At first the response was disregarded. Then came denial that the attack had value because it was based upon dog-work and the disease could not be reproduced in animals and, therefore, this work had no application to the disease in humans. Now comes condemnation of our work because the surgical operation is being applied successfully to patients. To those who built this cardboard superstructure our attack is illegitimate. It is illegitimate because it is based upon dog-work (about 6,000 experimental operations on the coronary blood vessels of dogs). It is also illegitimate because it is not based upon the electrocardiogram. Understanding of coronary heart disease, according to the clinician, is not possible by animal experimentation nor is it possible without the electrocardiogram. This is the credo of the internist. In making these declarations, he sacrifices the assets of restraint, logic, and science. A past president of the American Heart Association stated that he was going to keep the surgeon in his place concerning this disease. These are scarcely the words of a scientist. The time has come to make appraisal of these activities.

Acute Indigestion—The Attack of The Heart: Every age, including our own, knows so much that isn't so. Confident of what we know and oblivious to what we do not know, we face the present with complacency. Recently we changed a misconception concerning gravity when something was thrown off the earth and it did not come back. In the 1912–18 period another misconception was changed. This misconception concerned a disease which killed many people. The seat of this disease was changed from the stomach to the heart. In those days there were brilliant clinicians and pathologists but then, as now, they knew so much that wasn't so. Today there are misconceptions concerning this disease and to find these misconceptions we need scientists who demand a statement of the problem in simple terms and assessment of the evidence relating to the

problem. The change in location of the disease was of elemental importance but from our present point of view it scarcely required deep thinking. This change in location had no effect on treatment. The thinking concerning this disease was and is an incomprehensible superficiality.

After locating the disease in the heart, the term "heart attack" came into existence. Although this became a common term, it is not a scientific term and it is not defined in the medical dictionaries. When the disease kills, the term fatal heart attack is used. This term although it pertains to death, has no meaning concerning the mechanism by which death occurs. Indeed, the death factors of the disease are scarcely understood, and while the disease has been moved above the diaphragm it continues to be designated by non-scientific terms. The disease has not been moved far from where it was and our understanding of it has not been much improved.

Electrocardiogram: This has done much good; it also has done harm. Its value as a diagnostic aid and as a tool for study of various cardiac conditions needs no comment. The harm came when the electrocardiogram became an end in itself, when it became more important than the disease it was supposed to serve. This shift in importance can be illustrated by the following story: There was an important message which had to be delivered from one country to another. This message could not be entrusted in writing; it had to be delivered verbally. The only way the message could be delivered was by a long, dangerous journey over the desert. This required a messenger and the only transportation was by camel. The first night out the rider pitched his tent and protected himself from the elements. The second night out the rider pitched his tent, but by this time the camel felt his importance. He decided that he would occupy the tent. The tent was not large enough for both so the camel entered the tent and kicked his rider out. The rider and his message perished in the elements. The subject of coronary heart disease was investigated by the electrocardiogram, while other more important aspects of the disease were neglected. These other aspects like the rider and his message were lost to a vehicle of secondary importance.

Several additional points of criticism can be made concerning the electrocardiogram. One concerns its use or abuse as a therapeutic agent. It helps to treat the patient's psyche and for this purpose it is repeated over and over again. Not being informed about this, the patient does not object to these oft repeated records and believing that they help him, he is willing to pay for them. The electrocardiogram lends assurance to "the pat on the back"; it makes the patient secure in his belief that he is receiving treatment, and is doing well. The electrocardiogram therefore serves several purposes.

Medicaments: These give temporary relief of pain. The mechanism (pharmacologic or physiologic) by which this is accomplished is not known, but the most likely explanation is that they provide additional blood to ischemic muscle. Measurements in the experimental laboratory have not demonstrated this mechanism but it may be that the methods of measurements are not sufficiently delicate to measure small quantities that are clinically beneficial. On the basis of our work it can be stated that quantities in the range of drops or a few cubic centimeters per minute delivered to ischemic muscle are beneficial. The beneficial effect of these drugs is transitory. They do not change the anatomy of the crippled coronary circulation nor do they produce intercoronary arterial anastomoses. There are instances in which these drugs have no beneficial clinical effect and occasionally they lose their effectiveness. There is no explanation for this.

The reaction of the patient to his pills is that of expectation. When they produce temporary relief of pain he expects them to help cure his disease. He has additional reason for expectation because his physician prescribed them. When he finds out that they have not treated his disease he is not only disappointed but resentful because this information was withheld from him. The discovery that the medical treatment has failed is made by the patient and not by the physician. Except for its psychologic aspects, medical treatment is a failure. To those who built up this medical colossus, failure is unreal and impossible. It is so perfect that there is no need to search for other forms of treatment. It has withstood the impact of death, of thou-

sands and thousands of deaths. This has been accomplished by negating any other form of treatment. Surgical treatment has been negated in an absolute manner. If this had not been done this superstructure would begin to crack and questions would be asked concerning surgical operation.

The relationship between the physician and his dead patient is one of complacency. The death is unfortunate but "that is the way of the disease. It kills." There are many treatments for the disease but at the time of death one is never weighed against the other, and there is no question, no argument concerning the effectiveness of the treatment received by the patient. In this respect the role of the physician is similar to that of the high priest. Each is perfect in his behavior. The fact that the physician can absolve himself of all responsibility for death indicates that his treatment is not effective.

Substitutions for the Science: With so little to do in treatment and with so many people trying to make contributions, it is reasonable that substitutions for the science should arise. Many of these concern refinements in the electrocardiogram under a variety of conditions. A variety of treatments also have been advocated as follows: the abdominal belt, the chair treatment, the bed treatment, the bicycle treatment, and so on. None of these adventures puts blood in ischemic muscle.

In order to hold onto the patient it is important to minimize the danger of his disease. This approach has not been neglected by the medical cardiologist. He has told us that the disease is of little importance. Indeed, we are told that you might as well go ahead and have your occlusion and get it over with because while it might slow you up a bit it will make a better business man out of you. These statements are reminiscent of "laudable pus", an expression used before the time of Lister. The cardiologist denies that operation helps the patient. In so doing he speaks without knowledge. It is important now to analyze the purposes of such statements.

Round Table Discussions: It is customary these days for the internists to put on round table discussions at medical meetings concerning "myocardial infarction." These discussions by the internists cover a wide variety of subjects such as cholesterol, diet, obesity, the electrocardiogram, and anginal pain. It is not important that these discussions are not limited to death of muscle as indicated by the title. Sometimes a mild occlusion is defined and the way to make a diagnosis of a mild occlusion is presented. Sometimes a mild occlusion kills, and when a mild occlusion kills, the mechanism of death is a mystery. In the first place death should not have occurred with a mild occlusion; otherwise the terminology is wrong. In the second place the internist cannot explain the physiology responsible for the death. He does not know that the heart can electrocute itself without any death of muscle. He is not familiar with the theory of oxygen differentials and the electrical condition thereby produced. This should be elementary knowledge. He should know that there is no such thing as a mild occlusion.

Another subject not included in these round table discussions is the axiom of coronary artery disease. This also is an elementary idea and should be the starting point for therapy. The axiom is that after occlusion or stenosis of an artery, the fate of the patient depends upon the amount of blood in the ischemic muscle. If a certain amount is present the patient lives; if less than a certain amount is present the patient dies. Addition of blood is beneficial; reduction of blood has the opposite effect. It is incomprehensible that the internist has not concerned himself with this starting point in therapy. Perhaps he knew that to change blood supply was beyond his reach.

Recently an internist who is a popular speaker at medical meetings discussed the relationship between angina pectoris and tic douloureux. The relationship was that they were different kinds of pain. The medical audience never knows what the specialist will present at these meetings. At a recent round table discussion two internists discussed the relationship between coronary artery disease and sex. This discussion consumed so much time that little time was left for discussion of the new physiology of the disease. At the present time there are so many aspects to the disease that the internists can go on for a long time with their discussions. The writer suggests that discussion of coronary heart disease, in the future, be limited to physiol-

ogy and treatment, and that treatment be limited entirely to effect upon blood supply. The subjects of biochemistry, diagnosis and the electrocardiogram do not concern therapy and should be dealt with separately. There are new and important physiological concepts to be learned and assessed, and to society the disease has lost none of its importance. Treatment should involve high responsibility. It should be based upon the best knowledge now available. There is much to learn and there is much important research to be done and the internist should reorientate himself so that he becomes a part of the science and not an antagonist to it.

Science from the Laboratory: In the laboratory our answer to every question was determined by what we observed in the experiment. All preconceived ideas were destroyed if they were not supported by experiment. We made many misinterpretations of experiments but we always had the energy to carry on and to right ourselves. We also investigated blind alleys and we learned by these experiences. The end result of this work is an enormous experience. The knowledge and the facts refined from this work will be presented briefly.

(1) The axiom of the disease was defined. It concerns the amount of blood in ischemic muscle and is the starting point for any kind of effective therapy. We know by experiment that 300 ml/hour delivered to ischemic muscle protects the life of the dog when a ligature is placed around the descending ramus of the left coronary artery and 390 ml protects when the circumflex ramus is ligated. The heart beat is maintained by these quantities of blood. These quantities of blood must be available to the muscle distal to the ligature and can be measured by cutting the artery and letting the distal end bleed. Anything that can be done to increase this amount of blood is beneficial and this is the key to effective treatment. This is nothing more than a common-sense point of view, yet it has been neglected by the medical cardiologist.

(2) A uniformly well oxygenated heart is electrically stable.

(3) A uniformly cyanosed heart is electrically stable. Cyanosis can be produced by asphyxia, by clamping the intratracheal tube in the anesthetized dog. Oxygenated blood or the lack of it is not a factor in the electrical condition of the heart provided its distribution is uniform throughout the substance of the heart. A blue baby has a stable heart.

(4) Cyanosed muscle in juxtaposition to well oxygenated muscle produces electrical instability. The heart may fibrillate. Ligation of an artery produces this condition.

(5) Well oxygenated muscle in juxtaposition to cyanosed muscle produces electrical instability. The heart may fibrillate. Cannulation of a coronary artery and perfusion of it with well oxygenated blood in a heart that is cyanosed by asphyxia as in item 3 produces this condition.

(6) Electrograms taken from the surface of the heart under conditions referred to in items 4 and 5 show elevation of the S-T segment over the cyanosed muscle and depression over the well oxygenated muscle. The electrical condition produced in these experiments is related to oxygen-differentials. Placing pink and blue muscle in juxtaposition is not related to injury and "current of injury" by the physiologists is not correct. A child with one coronary artery arising from the pulmonary artery and one arising from the aorta has anginal pain and an unstable heart. A checker-board distribution of oxygenated blood produces instability and fibrillation.

(7) Coronary artery occlusion produces: (a) electric instability, (b) death of muscle. Fibrillation may occur without death of muscle. Death of muscle may occur without fibrillation. These are separate, unrelated biological phenomena.

(8) An even distribution of blood in the heart reduces the severity of the two phenomena in item 7. The production of an even distribution is one approach to treatment of the disease.

(9) Addition of blood to ischemic muscle is the other approach to treatment.

(10) Quantities of blood as small as 2, 4 or 6 ml/min give significant protection to the heart when delivered to ischemic muscle. Recognition of this fact is essential in understanding and accepting effective therapy of the disease.

(11) Intercoronary channels aid in produc-

ing even distribution. These can be produced by surgical operation.

(12) The heart resists addition of blood. Perhaps the methods that have been investigated and used in the past can be improved in the future.

(13) Intercoronaries can be produced by the following surgical procedures—abrasion of surface of heart and lining of parietal pericardium, a light application of 5 per cent aqueous solution of trichloracetic acid to the surface of the heart between the coronary arteries, a light sprinkling of powdered asbestos on the surface of the heart, narrowing of the coronary sinus to a diameter of 3 mm, application of parietal pericardium and its outside fat to the surface of the heart as a graft. If the human heart is irritable at operation and if the coronary sinus is difficult to expose some of these steps in the operation are omitted.

(14) Operation under item 13 makes it possible to utilize the heart's own blood in the most beneficial way. It makes it possible for a red cell once it gets beyond the stenosis in the artery to go anywhere within the substance of the heart where it can do the most good. It does not add to the total coronary inflow to the heart but it does add to the amount available to ischemic muscle. It is brought into the ischemic area from adjacent areas. When the circumflex artery is ligated, 4.7 ml/min or 282 ml/hour are brought into the ischemic muscle from the right coronary artery and from the descending ramus of the left coronary artery. This quantity is added by operation to the quantity that normally exists in the ischemic muscle and brings the total quantity up to 8.5 ml/min.

(15) This addition of blood reduces mortality when a test artery is ligated. In normal dogs the mortality following ligation of the descending ramus of the left coronary artery at its origin in one step is 70 per cent. In dogs in which this operation was done weeks or months prior to test artery ligation the mortality is 26.6 per cent. Operation reduces mortality 43.4 per cent.

(16) Operation reduces the size of the infarct 60 to 70 per cent in dogs under item 15.

(17) Electrocardiographic alterations are less severe in these protected dogs.

Laboratory and Clinical Concepts Brought Together: Facts from the laboratory have thrown new light on the disease. The death factors in the disease have become better understood. An analysis of these factors makes it possible to understand what is necessary for treatment of each. Such understanding indicates what can be done and what cannot be done in treatment of the disease.

(18) One of these factors is self electrocution of the heart as indicated in item 4 of the experimental work. It may occur in the presence of only slight anatomic damage in the heart. This factor may occur when the clinical diagnosis is a mild occlusion or a mild attack and this produces confusion. Because this factor may appear under these conditions it is advisable not to use the term mild attack or mild occlusion. These terms refer to anatomic damage in the heart whereas this death factor is physiologic in nature. This factor also appears in the presence of severe disease in arteries and muscle. It is a common cause of death.

(19) This death factor may be reversible as shown by two patients who fibrillated and in whom a coordinated beat was restored. These patients are alive three years and one year later. These experiences indicate that anatomically the heart, in the absence of severe disease, is capable of continued function and that this death factor may be a small factor.

(20) This death factor can be prevented as in items 13 and 14. Prevention was established in the laboratory but it applies also to humans. It is the most effective treatment for anginal pain and it also prolongs life.

(21) The second death factor is inadequate arterial inflow. There is not enough blood to support the heart beat. The muscle may or may not be extensively damaged. Any slight manipulation of the heart at operation is followed by asystole or fibrillation. The patient may have little energy. He may not tolerate certain positions in bed as though position might pinch off small inflow in a diseased artery. This condition is difficult to recognize clinically.

(22) Treatment of this factor requires more blood. This might be accomplished either through the diseased arteries or from outside

sources. So far not very much has been accomplished along these lines. We put in blood backwards through the venous system. We tried to add blood from grafts on the heart including the mammary arteries. We also tried to clean out the coronary arteries and also to place shunts into them. Others are working on these developments. Perhaps something more effective will be developed in the future and this work should be encouraged. Patients with severe inflow reduction are not candidates for the author's operation.

(23) The third death factor is insufficient muscle to maintain the circulation. One artery after another becomes blocked off; one segment of muscle after another is destroyed. While these destructions are taking place the heart beat is preserved and the process of destruction has time to continue. The total arterial inflow may be adequate to support the heart beat. The patient ultimately dies in failure.

(24) Treatment of failure is the only therapy. The scars cannot be converted into good muscle. These patients are not candidates for any kind of operation for this disease.

(25) The best patient for the author's operation is the one with maximum of pain and minimum of disease.

Conclusions: This presentation is the author's point of view concerning coronary heart disease. Some of it will prove to be wrong in the future but this is expected.

Effective treatment of this disease cannot continue to be "a dead issue." Research in treatment (aside from biochemistry and prevention) must necessarily be done. This presentation gives some direction for future research. Opposition must dissolve into cooperation. This presentation should accomplish some good if for no other reason than that it challenges ideas that have been given sanctuary from attack in the past.

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Clinical Studies

Aortic Stenosis*

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AORTIC stenosis is a simple mechanical fault, which, if severe enough, imposes a heavy burden on the left ventricle and sooner or later overcomes it. An obstructive lesion of this sort presents an obvious challenge to the surgeon. The object of this paper is to describe just how far this challenge has been met, and of necessity it presents a physician's point of view.

MATERIAL

The facts offered have been obtained by analysing a consecutive series of 250 cases of aortic stenosis under the author's personal observation over the last seven years. Cases with dominant mitral valve disease have been excluded although they may be alluded to in the text. The series was made up as follows:

Trivial aortic stenosis	16
Congenital aortic stenosis (with or without incompetence)	54
Rheumatic aortic stenosis (absent or trivial incompetence)	150
Rheumatic aortic stenosis (with serious incompetence)	30

Of the 150 well-developed cases of relatively pure rheumatic aortic stenosis, 128 (85 per cent) were severe enough to have symptoms, 10 were severe but so far without symptoms, and 12 were relatively mild.

In contrast, of the 54 congenital cases only 15 (28 per cent) had symptoms, 10 were severe but so far without symptoms, and 29 were relatively mild.

In the absence of symptoms the simplest definition of severe stenosis is one with sufficient hypertrophy of the left ventricle to cause inversion of the T wave of the electrocardiogram in left ventricular surface leads or their equivalents.

Frequency: These 250 cases were studied over a period of seven years, and during the same span 78 cases of pure rheumatic aortic incompetence and about 700 cases of mitral valve disease were seen. Amongst the rheumatic cases aortic valve disease (278 cases) was therefore 2.4 times less common than mitral valve disease, and well developed aortic stenosis (150 cases) twice as common as pure incompetence.

ETIOLOGY

As previously indicated, about 20 per cent of the total cases were congenital and the rest rheumatic. Of the congenital cases more proved to be subvalvular than originally suspected. In view of the diagnostic difficulty exact figures cannot be given, but operative experience suggests that at least one-third are subvalvular.[4] Three out of nine surgical cases in the present series were subvalvular.

Of the presumed rheumatic cases 44 per cent gave a history of the rheumatic state in childhood, adolescence, or early adult life. This supports the view of Karsner and Koletsky,[11] based on micropathology, that acquired aortic stenosis is nearly always rheumatic. It should be remembered that a rheumatic history is obtained in only 60 per cent of all cases of mitral stenosis.

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Pathology

Initial fusion takes place at the commissures and over the years gradually involves the free margins. This slow process may depend on the deposition and organization of minute thrombi as suggested by Margarey in respect of mitral stenosis.[17] By the time aortic stenosis is severe enough to cause symptoms the valve is commonly thick, distorted, and more or less ankylosed. By means of a cinephotographic technic McMillan has shown very clearly how these valves function.[15]

In the present series calcification occurred in no less than 80 per cent of all cases over the age of 30 (86 per cent of the males and 50 per cent of the females).

According to Dry and Willius[8] both the frequency and severity of coronary atherosclerosis are inversely proportional to the degree of stenosis. Aortic atheroma bears a similar inverse relationship to aortic stenosis.[6]

The left ventricle hypertrophies but does not dilate significantly until heart failure sets in.

Hemodynamics

As demonstrated by Wiggers[20] the aortic orifice must be reduced to about one-quarter of its natural size before significant changes in the circulation occur. McMillan, Daley, and Matthews[16] showed that the normal aortic valve orifice was triangular. Since the internal diameter of the aortic ring averages about 2.6 cm, the triangular orifice must measure about 3 sq cm (McMillan).[15] Physiological stenosis thus implies an orifice having an area less than 0.75 sq cm or less than a 1.5 x 1.0 cm oval as estimated surgically. Anything larger than this is physiologically unimportant.

The hemodynamic effects of critical stenosis (aortic valve area less than one-quarter of its natural size) may be enumerated as follows:

(1) An increase in the amplitude of the *a* wave of the left atrial pressure pulse (Fig. 1) as described by Gorlin *et al.*[10]

(2) Elevation of the presystolic left ventricular tension resulting from the giant *a*, and elevation of the maximum left ventricular systolic pressure (Fig. 1).

(3) A systolic pressure gradient across the aortic valve measuring between 5 and 200 mm Hg according to the severity of the stenosis and the forward stroke flow (Fig. 2).

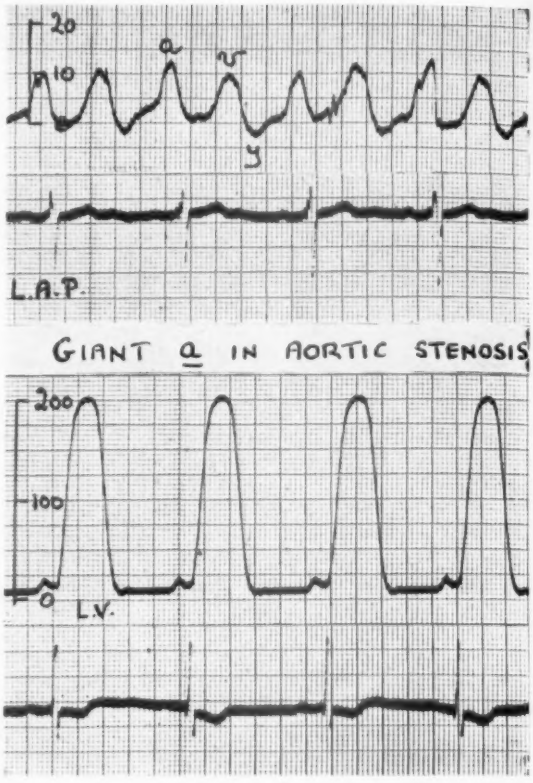

Fig. 1. Giant A wave in left atrial pressure pulse (upper tracing) raising the end diastolic tension in the left ventricle (lower tracing) in a case of aortic stenosis.

(4) A slow rising central aortic pressure pulse with a low anacrotic notch, reduced maximum pressure and prolonged ejection phase (Fig. 2).

(5) A slow rising peripheral pressure pulse rather similar to the aortic, but with a higher anacrotic shoulder (Fig. 3).

(6) A limited cardiac output which becomes reduced at rest with the onset of heart failure.

(7) An inadequate coronary blood flow to meet the increased metabolic demands of the overworked left ventricle.

Clinical Features

Age: Excluding the 16 cases of trivial stenosis and the 54 congenital cases, most of which were children, the age of the remaining 180 rheumatic patients ranged between 19 and 79 years and averaged 46. Since over 90 per cent of these 180 cases were severe, it is clear that

rheumatic aortic stenosis is not a disease of old age.

Sex: The male to female sex ratio was 2 : 1, which is the same as that reported by Mitchell *et al.*[18] in their series of 533 cases. When patients with mitral stenosis as well were included this ratio fell to 1.5 : 1.

SYMPTOMS

Angina Pectoris: Angina occurred in no less than 70 per cent of those cases severe enough to have symptoms of any kind. In quality, distribution, duration, and relationship to effort it differed in no way from that associated with coronary disease, and it was similarly relieved by trinitrin. Amyl nitrite should be avoided for it may induce syncope in severe aortic stenosis. The total duration of angina ranged between three months and seven years, apart from six exceptional cases (5 per cent) in which it had occurred over remarkably long periods (10 to 20 years).

As a rule, stenosis was advanced when angina was present, but this was not so in 10 per cent of those with this symptom, and could not have been so at the onset in the six cases just mentioned. In the milder group the sucking effect of the aortic jet may have been chiefly responsible for the inadequate coronary flow; coronary disease could not be invoked in these relatively mild cases, for some of them were young women and they did not follow a coronary course. In the whole series there was no single instance of coronary thrombosis.

Syncope: Syncope on effort occurred in one-third of those with symptoms. Three-quarters of these cases also had angina. Again, 10 per cent of syncopal cases could not be classed as severe on other grounds. The symptom has been attributed to acute left ventricular failure or to a fixed low cardiac output, so that the blood pressure cannot be maintained when sufficient vasodilation occurs in muscle. Amyl nitrite may induce syncope in aortic stenosis, as previously mentioned.

Dyspnoea: Simple effort dyspnoea was relatively uncommon. When breathlessness developed it usually signalled the onset of left ventricular failure, and this occurred in 45 per cent of those with symptoms.

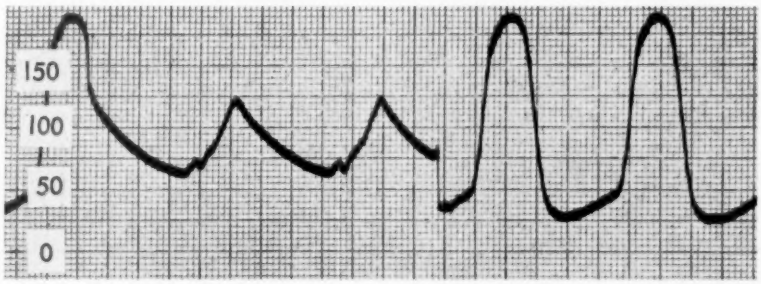

Fig. 2. Immediately consecutive central aortic and left ventricular pressure tracing in a case of aortic stenosis, showing a pressure gradient of 65 mm Hg, an extremely low anacrotic notch in the aortic tracing and prolonged ejection.

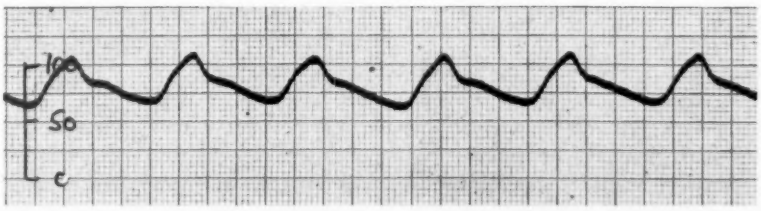

Fig. 3. Brachial artery pressure pulse in a case of aortic stenosis showing a slow ascent, higher anacrotic shoulder (compared with the aortic pressure pulse) and a delayed maximum pressure (0.26 sec) measuring only 110 mm Hg.

"Congestive failure" with a raised venous pressure, hepatic enlargement, and edema occurred in 15 per cent of those with symptoms.

PHYSICAL SIGNS

Trivial Stenosis: The only physical signs of trivial aortic stenosis are a loud aortic ejection click, followed by a mid-systolic murmur, as described by Leatham[12] and others. Both click and murmur were often well heard over the left ventricle at the apex beat. Many cases of alleged functional mitral systolic murmur are really due to trivial aortic valve disease.

One-quarter of these very mild cases gave a previous history of rheumatic fever. Since a number of patients with advanced stenosis gave a history of an alleged functional systolic murmur during World War I, it is concluded that trivial stenosis may require about 40 years in which to become severe.

Brachial Pulse: The classical aortic stenotic pulse is anacrotic. According to the Oxford English Dictionary this word is an abbreviation of anadicrotic (twice beating on the upstroke). By common use it has come to mean a small slow rising pulse with a perceptible notch, hesitation, or shoulder on the ascending limb (Fig. 3).

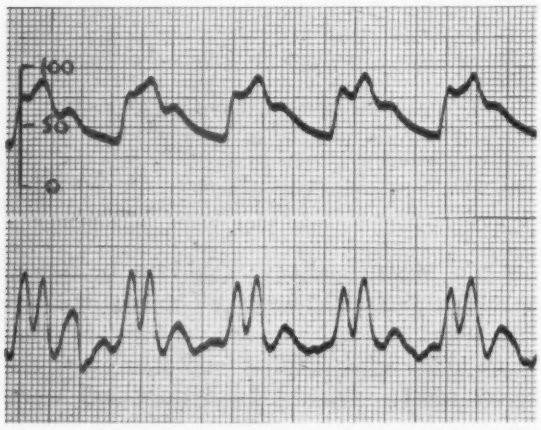

Fig. 4. Pulsus bisferiens. The upper tracing is direct, the lower indirect; the latter more closely represents what is felt by palpation.

The bisferiens (twice beating) pulse refers to the palpably double systolic wave caused by a combination of aortic stenosis and incompetence (Fig. 4). The small trough which separates the two waves may represent the sucking effect of a powerful jet on the lateral aortic pressure as suggested by Fleming.[9] No case with an unquestionable bisferiens pulse proved suitable for valvotomy; the aortic valve area was always too large and the amount of incompetence too great.

The *systolic brachial blood pressure* was usually low, the mean of all severe cases being 120 and the range 90 to 170 mm Hg (Fig. 5). It is

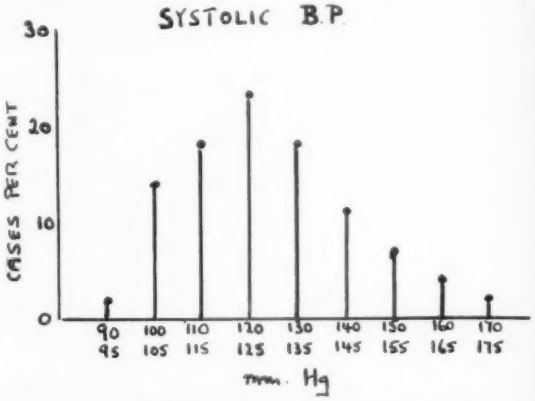

Fig. 5. Frequency distribution of the level of the systolic blood pressure in severe aortic stenosis.

extremely rare for a case of severe organic aortic stenosis to have a systolic blood pressure of 200 mm Hg or more under any circumstances.

The *pulse pressure* averaged 43 mm Hg, and was below 40 in 30 per cent of critical cases; the usual range was 30 to 50 mm Hg.

When there was an important degree of associated aortic incompetence the systolic pressure was usually higher, ranging between 130 and 180, and the pulse pressure averaged 72 mm Hg. This harmonizes with standard teaching.

Carotid Pulse: We learned that a conspicuous carotid pulse always meant too much aortic incompetence to warrant valvotomy; that in severe stenosis the carotid pulse was invisible. Failure to appreciate this simple truth led to ill advised valvotomy on more than one occasion.

Cardiac Impulse: Aortic stenosis must be very advanced before there is appreciable displacement of the apex beat; the common cause of an obvious shift to the left was left ventricular failure. The cardiac impulse is left ventricular in type, and quietly heaving in character, but

it is not hyperkinetic (tumultuous) as in aortic incompetence. It reflects hypertrophy rather than overfilling. The term hemodynamic might be properly applied to it.

Auscultation: There are four important auscultatory signs of aortic valve disease—the aortic ejection click, the aortic ejection murmur, delayed aortic valve closure, and the aortic diastolic murmur (Fig. 6).

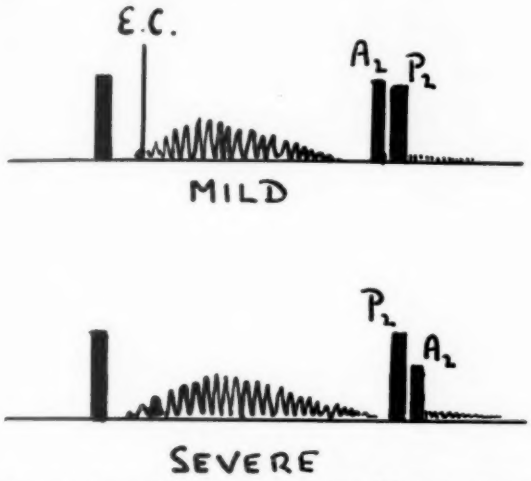

Fig. 6. Auscultatory features of mild and severe aortic stenosis. E.C., aortic ejection click; A_2, aortic component of the 2nd sound; P_2, pulmonary component of the 2nd sound.

A sharp *aortic ejection click* (Lian and Welti[14]) occurring about 0.08 sec after the mitral first sound, was heard in 75 per cent of mild or moderate cases, but in only 25 per cent of severe cases. It was not influenced by valve calcification. When heard over the left ventricle at the apex beat it must not be confused with with left atrial gallop.

An *aortic ejection murmur* of moderate to gross intensity was heard in all cases at apex and base. As described by Leatham[12] it was typically mid-systolic, starting with the ejection click when present and stopping in protodiastole before the aortic second sound. Since the latter is delayed in severe cases the murmur may be relatively long, and if the pulmonary component of the second heart sound is alone audible it may be confused with the pansystolic murmur of mitral incompetence; but its later onset and crescendo-decrescendo quality help to prevent error. It should be understood that ejection murmurs end with the protodiastole of the related ventricle, i.e. with the onset of ventricular relaxation 0.02–0.04 sec before closure of the related semilunar valve. In severe aortic stenosis A_2 may be sufficiently delayed to fall 0.03 second after P_2, in which case the aortic ejection murmur ends with P_2. Only in the absence of incompetence and heart failure is the length of the murmur related to the severity of the stenosis.

The murmur was accompanied by a *thrill* in 80 per cent of cases. The thrill was usually absent in trivial cases and often absent when the cardiac output was low, as in advanced congestive failure. *A thrill provides no evidence of critical stenosis*, for it was present and usually florid in 90 per cent of those cases with both stenosis and incompetence in which the latter was dominant; in six of these cases an ill advised attempt at aortic valvotomy or subsequent necropsy proved that the valve orifice measured appreciably more than 0.75 sq cm. On the other hand, in the absence of incompetence an aortic systolic thrill was not felt unless the stenosis was at least moderately severe. It is concluded that an increased forward stroke flow is necessary to produce a thrill in the absence of well developed stenosis.

The *2nd heart sound* was normal in 5 per cent, single in 70 per cent, and paradoxically split in 25 per cent. When a single 2nd heart sound could be well heard over the left ventricle at the apex beat or over the carotid, it was attributed chiefly to the aortic component; when it could be heard only at the base it was attributed to pulmonary valve closure and the aortic component was believed to be absent. An absent aortic 2nd sound so defined was recorded in only 20 per cent of cases. Thus closure of heavily calcified valves was usually audible.

Reversed or paradoxical splitting of the second sound is due to delayed aortic valve closure. Normally the aortic valve closes before the pulmonary, and a split second sound widens on inspiration, because increased right ventricular filling delays the pulmonary element. When the aortic valve shuts after the pulmonary valve, a split 2nd sound closes on inspiration (Leatham[13]). Delay in aortic valve closure in the

absence of left bundle branch block is due to prolonged ejection. Although reversed splitting of this kind was heard in only 25 per cent of cases it was recognized more frequently with the help of phonocardiography.

An *aortic diastolic murmur* was heard in one-third of the congenital cases, whether valvular or subvalvular, and in two-thirds of the rheumatic. Its presence in subvalvular stenosis was surprising, for in these cases the valve itself was found to be normal. Dilatation of the aortic ring was presumably responsible. In mild cases in which the basis for an aortic systolic murmur may be in doubt, a diastolic murmur provides excellent evidence of organic aortic valve disease. It was loud in only 10 per cent of cases in which it was heard. As a rule, a loud diastolic murmur was associated with other features indicating serious incompetence, but not necessarily.

Physiologically dominant aortic incompetence complicating cases of aortic stenosis encouraged the ejection click and increased the intensity of the systolic murmur and thrill; overfilling of the left ventricle helped to prolong the ejection phase, so that A_2 was still delayed; paradoxical splitting of the 2nd sound thus provided no evidence of dominant stenosis.

ELECTROCARDIOGRAM

The electrocardiogram was normal in all trivial and most moderate cases, but was never normal in severe cases. In these, left ventricular preponderance was considerable (with T wave inversion) in 80 per cent, moderate in 3 per cent, and slight in 3 per cent; in the remaining 14 per cent there was left bundle branch block.

Atrial fibrillation occurred in 13 per cent of the rheumatic cases, all of which had associated mitral valve disease. It occurred in none of the congenital cases.

The electrocardiogram in cases with dominant aortic incompetence tended to be less florid in proportion to the severity of the lesion.

X-RAY APPEARANCES

A relatively small aortic knuckle and post-stenotic dilatation of the ascending aorta were typical (Fig. 7). Three-quarters of those with

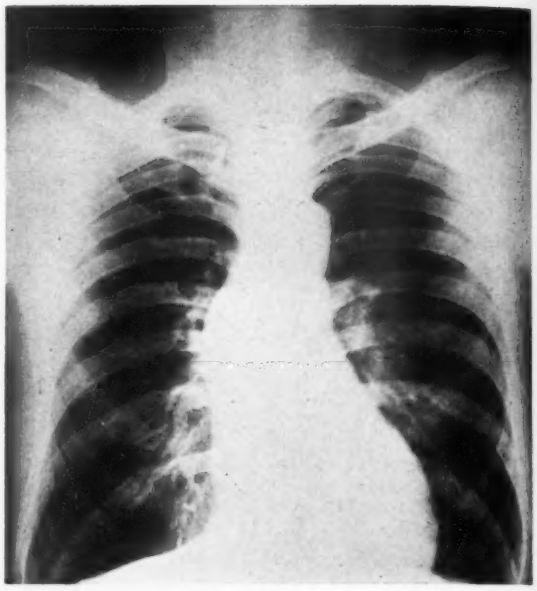

Fig. 7. Typical skiagram of a case of aortic stenosis showing post-stenotic dilatation of the ascending aorta and hypertrophy rather than dilatation of the left ventricle.

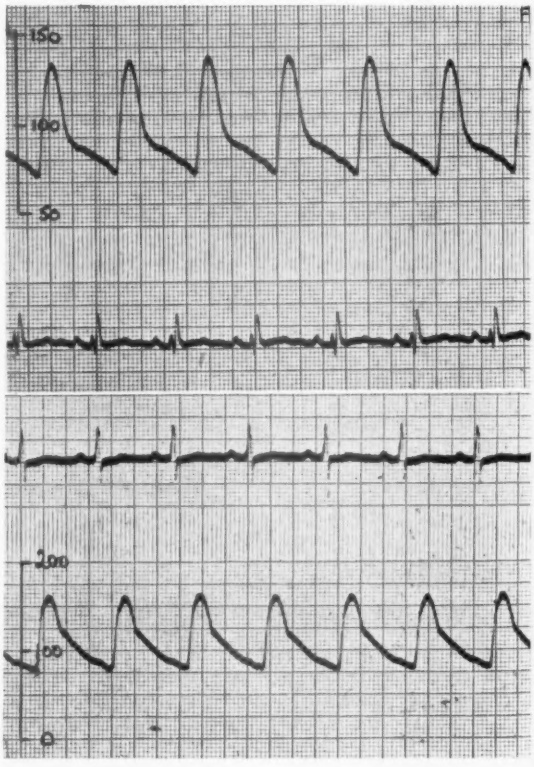

Fig. 8. Normal direct pressure tracings from the femoral (upper tracing) and brachial (lower tracing) arteries in two normal subjects.

Fig. 9. Direct brachial arteriogram in the case of severe aortic stenosis showing a slow initial ascent (500 mm Hg per sec), relatively low anacrotic shoulder (65 per cent of maximum pressure), delayed maximum pressure peak or "tidal" wave 0.26 sec after the onset, low systolic blood pressure (100 mm Hg), delayed dicrotic notch at 0.36 sec, and absence of a positive dicrotic wave.

considerable left ventricular enlargement had left ventricular or congestive heart failure. In the absence of failure severe aortic stenosis may be associated with a normal cardiothoracic ratio.

As mentioned previously, 80 per cent of cases over 30 years old, whether congenital or rheumatic, had calcification of the aortic valve, usually of considerable degree. It was more frequent in men (86 per cent) than in women (50 per cent). In respect of both the mitral and aortic valve, calcification was recognized more certainly by means of fluoroscopy than by palpation at operation, and tomography had little advantage over screening. Calcification of infundibular stenosis was not encountered with certainty.

In the group with combined stenosis and serious incompetence calcification occurred in only 50 per cent. The lower incidence could not be attributed to any difference in sex distribution.

Arteriograms

Brachial and Aortic

Normal Arteriogram: Intra-arterial pressure tracings were recorded from the brachial artery as a routine. In normal subjects (Fig. 8) the pressure rises rapidly from the onset to a high anacrotic shoulder at a maximum rate of 750 to 1,250 mm Hg per sec, averaging 1,000 mm per sec. The anacrotic shoulder is commonly reached in 0.08 sec; maximum pressure is achieved in an average of 0.13 sec ranging between 0.10 and 0.16 second when corrected for heart rate by dividing by the square root of the cycle length. As a rule there is but one peak, but sometimes there is a secondary peak, "tidal wave" or end-systolic shoulder preceding protodiastole. This occurs 0.20 to 0.24 sec after the onset when corrected for heart rate in the manner just described. Protodiastole follows, the pressure falling as the left ventricle relaxes, until the peripheral resistance is greater than that of the left ventricle, when the aortic valve closes and prevents back-flow. Aortic valve closure is represented by the dicrotic notch. In normal controls this occurs about 0.32 sec after the onset when corrected for rate (range 0.28–0.36). A secondary dicrotic wave may follow the dicrotic notch.

Arteriogram in Aortic Stenosis: In aortic stenosis the *anacrotic shoulder* is appreciably lower (Fig. 9), occurring on the average at a point

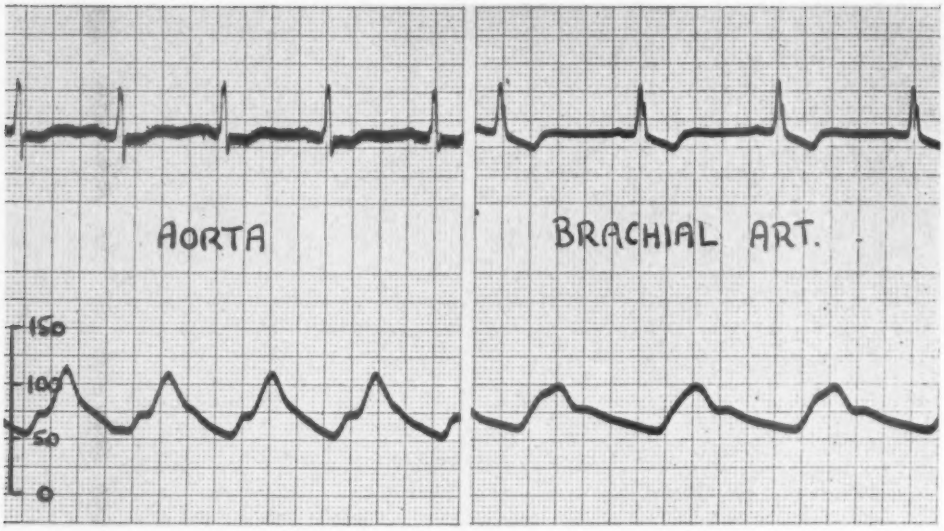

Fig. 10. Aortic and brachial pressure pulses from a case of aortic stenosis showing how the anacrotic notch rises as the pulse wave proceeds to the periphery. The rate of ascent from the onset to the anacrotic shoulder is the same and measures only 250 mm Hg per sec. The delay in maximum pressure (0.28 sec) and in the dicrotic notch (0.4 sec) is approximately the same in both tracings despite the difference in rate.

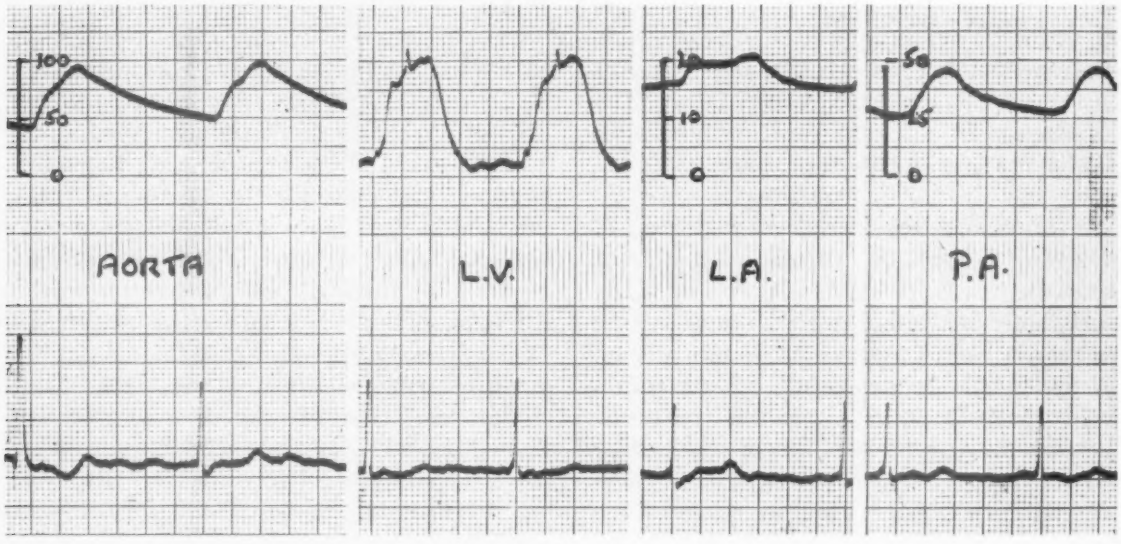

Fig. 11. A case of aortic valve disease with dominant incompetence showing the relatively high position of the anacrotic notch (50 per cent maximum pressure) in the central aortic tracing and the absence of a pressure gradient across the aortic valve. The maximum pressure is delayed, occurring 0.30 sec after the onset.

two-thirds of the way up the ascending limb (range 40 to 90 per cent of maximum pressure); as a rule the shoulder is much more pronounced than normal and justifies the term anacrotic notch. In central aortic pressure tracings the notch was always lower on the ascending limb (Fig. 10), very low when stenosis was severe (Fig. 2), as described by Wiggers,[20] and about half-way up the ascending limb in milder cases and in those that were complicated by serious incompetence (Fig. 11).

The more severe the stenosis the slower was the rise of pressure and the later was maximum pressure reached. In severe cases the pressure rose at an average rate of 450 mm Hg per sec from the onset to the anacrotic notch or shoul-

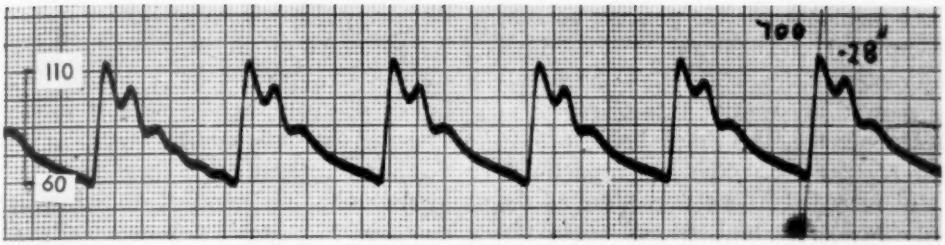

Fig. 12. Direct arteriogram showing pulsus bisferiens in a case of aortic valve disease with dominant incompetence. The percussion wave is higher than the "tidal" wave, the two peaks being separated by a trough. The rate of ascent from the onset of the first peak is rapid (800 mm Hg per sec), but the "tidal" peak is delayed (0.28 sec). Cardiac output was 5.2 l/min, and left ventricular pressure 175/15.

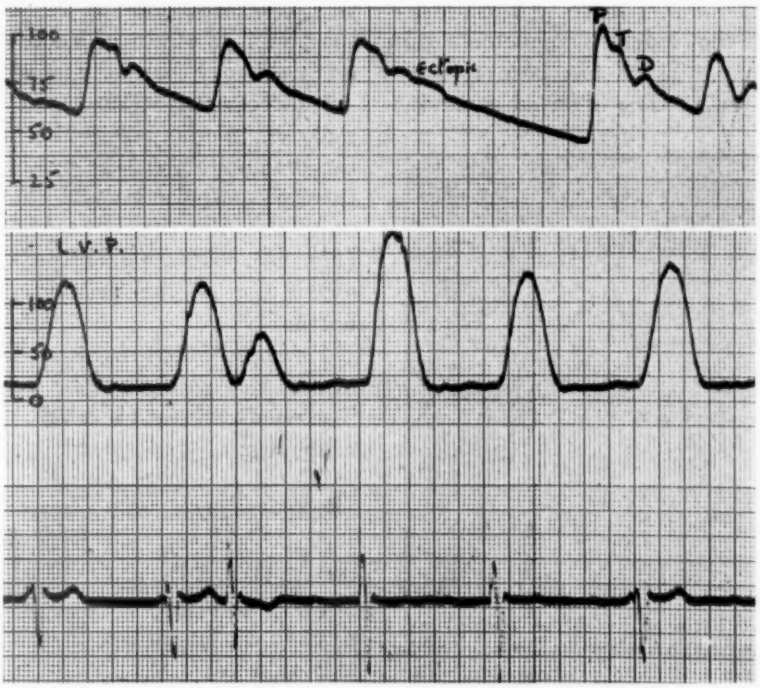

Fig. 13. Brachial arteriogram in a case of heart failure secondary to severe aortic stenosis showing the effect of increased ejection; in the stronger beat following the pause after the ectopic, when the initial left ventricular tension is higher (see lower tracing), the rate of ascent is faster, the percussion wave (P) is higher and the "tidal" wave (T) more conspicuous.

der, ranging between 200 and 750 mm Hg per sec. Maximum pressure was achieved in an average time of 0.23 sec from the onset, when corrected for rate by dividing by the square root of the cycle length; the range was 0.13 to 0.29 sec when so corrected.

The *dicrotic notch* was also delayed. Its average time was 0.37 sec after the onset when corrected for rate, representing a delay of 0.05 sec; but the range was considerable (0.32–0.46 sec). Phonocardiographic measurement of the timing of aortic valve closure demonstrates delay of similar magnitude.

A secondary dicrotic wave was rare in severe stenosis, but was seen occasionally when the cardiac output was very low.

The *pulsus bisferiens* (Fig. 12) was usually recorded by direct arterial puncture as an unusually flat, prolonged and fairly high anacrotic shoulder rather than two systolic waves separated by a trough. External pick-up devices, including the palpating finger, may record the

plateau as a momentary fall in pressure because of their upward momentum at the time. Typical direct pressure tracings of the pulsus bisferiens showed an average rate of ascent of 850 mm Hg per sec, the range being 625 to 1,440 mm Hg per sec. The anacrotic notch was usually recorded about four-fifths of the way up the ascending limb (range 66 to 100 per cent). Maximum pressure was reached in 0.14 to 0.27 sec when corrected for heart rate, or in an average of 0.19 sec.

As stated previously, the pulsus bisferiens proper always meant that there was too little obstruction and too much incompetence to warrant valvotomy. There has been no exception to this rule. The delayed summit, like delayed aortic valve closure in these cases, is attributed to prolongation of the emptying time of an overfilled left ventricle (from aortic incompetence) working against moderate obstruction (stenotic component).

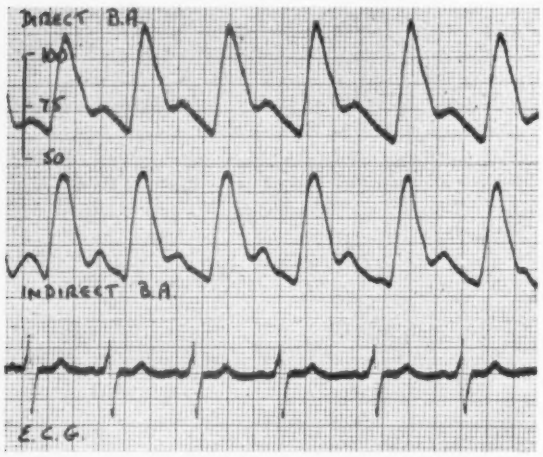

Fig. 14. Comparison between direct (top tracing) and indirect (middle tracing) arteriogram, showing similarity in wave form and time relationships. The delay of 0.03 sec in the direct tracing is due to time lag in the fluid system connecting the needle in the artery to the transducer (exceptionally long in this case).

The configuration of these brachial arteriograms may be modified to some extent by changes in cardiac output and peripheral vascular resistance. When the forward stroke flow increases, the speed of ascent quickens (Fig. 13) and the late peak is more conspicuous. When the forward stroke flow diminishes, these effects are reversed, so much so that during the period of strain of Valsalva maneuver the late peak may disappear altogether.[7]

Indirect arteriograms, recorded by means of a carbon microphone applied superficially over the brachial artery, are technically satisfactory in respect of the general configuration of the pulse and the timing of its component parts (Fig. 14), but not in respect of the speed of ascent nor of the position of the anacrotic notch.

Variations in arteriograms: Interpretation of direct arteriograms can be notoriously difficult. The chief variations in severe aortic stenosis are as follows:

(1) *A pronounced anacrotic notch* high up the ascending limb, the tracing resembling the pulsus bisferiens, but with a slower rate of ascent (Fig. 15).

(2) *Dwarfing of the tidal peak* by marked reduction of the stroke flow, so that the "percussion wave" or anacrotic shoulder becomes the summit of the pulse wave (Fig. 16). The slow rate of ascent, however, distinguishes this pulse from an otherwise similar type of tracing

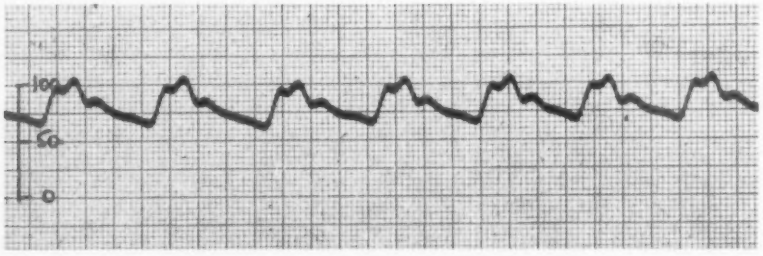

Fig. 15. A rare example of the pulsus bisferiens in a case of severe aortic stenosis. At operation the valve orifice measured only 4 x 2 mm. The slow rate of ascent from the onset of the anacrotic notch (312 mm Hg per sec) revealed the correct diagnosis. The positive dicrotic wave is also unusual. Left ventricular pressure was 150/10.

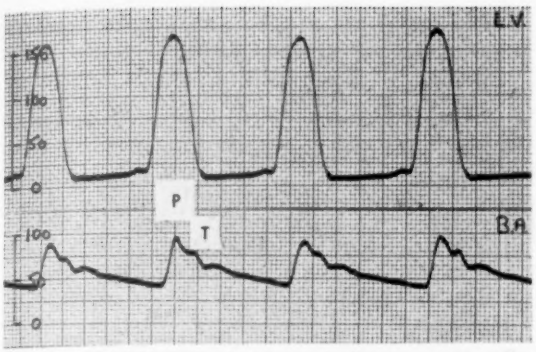

Fig. 16. Simultaneous left ventricular pressure pulse and brachial artery pressure tracing to show dwarfing of the tidal wave in the arteriogram as the result of a low forward stroke flow. The anacrotic shoulder, at 0.10 sec, is the maximum pressure peak. The tidal wave is late at 0.26 sec. The rate of ascent is 450 mm Hg/sec.

often seen in cases with dominant aortic incompetence (Fig. 17). When the "tidal" peak is dwarfed in this way measurement of the time taken for maximum pressure to be achieved is misleading, for it is then the "percussion" wave that is being considered, not the "tidal" wave.

(3) *Disappearance of the "tidal" peak*, due to an even smaller forward stroke flow results in a relatively sharp pulse wave with a single peak occurring at around 0.12 sec from the onset. The only clue to the real nature of this rare pulse is the slow rate of ascent (Fig. 18).

(4) *An unusual low and ill defined anacrotic shoulder* also results in a single pressure peak which at first sight does not suggest aortic stenosis (Fig. 19). The true nature of this pulse becomes evident, however, if the speed of the recording paper is increased to 50 mm/sec, as in the second tracing illustrated, when the low anacrotic shoulder can be identified; moreover, the ascent is slow (200 mm Hg/sec) and the single peak is late (0.22 sec after the onset when corrected for heart rate), and therefore represents the "tidal" wave. All these

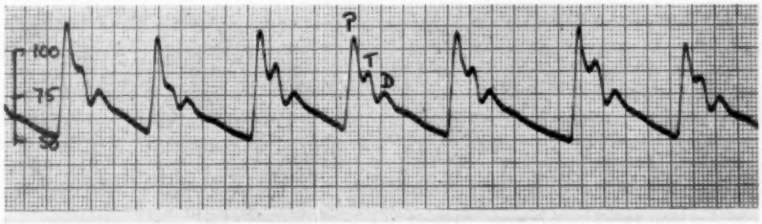

Fig. 17. Brachial arteriogram in a case of aortic stenosis and incompetence showing dwarfing of the tidal peak at 0.24 sec. The rapid rate of ascent (1,000 mm Hg/sec) shows that the incompetence is dominant.

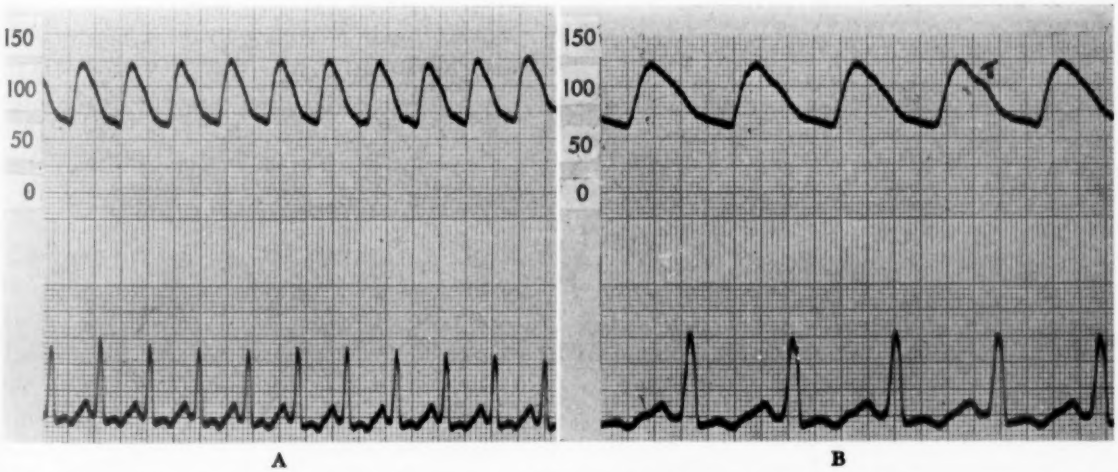

Fig. 18(A). Arteriogram from a case of severe aortic stenosis showing almost complete disappearance of the tidal peak. Maximum pressure is achieved relatively early and represents the anacrotic shoulder. (B) Same tracing with paper speed twice normal (at 50 mm/sec) to show submerged tidal wave (T).

changes become obvious enough when the pulse is compared with that obtained after valvotomy (Fig. 19).

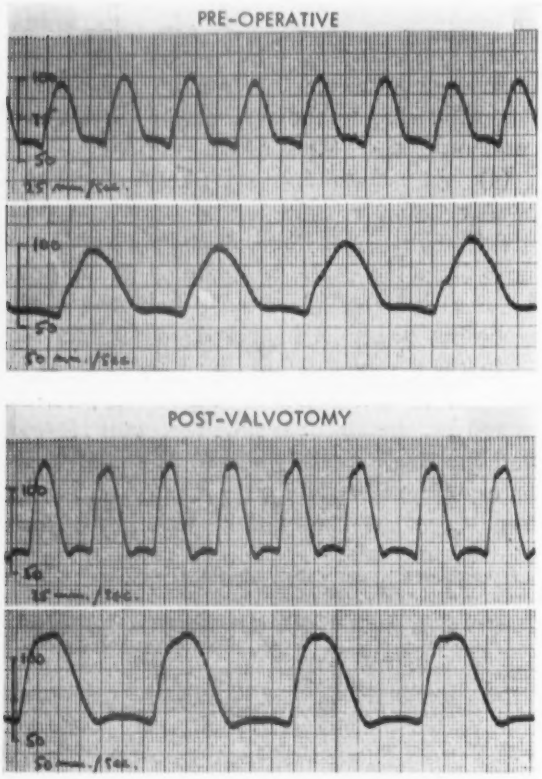

Fig. 19. Brachial arteriograms at speeds of 25 and 50 mm/sec in a case of severe aortic stenosis before and after valvotomy. The single peak is late and represents the tidal wave, the anacrotic shoulder being very low. After valvotomy the anacrotic shoulder has risen conspicuously and the rate of ascent has increased from 375 to 750 mm Hg/sec.

One of the difficulties in differential diagnosis is to distinguish a left ventricular cardiomyopathy from severe aortic stenosis when there is advanced heart failure. The small pulse of a severe cardiomyopathy may have a slow ascent occasionally (average 750 mm Hg/sec; range 450 to 1,375); maximum pressure is reached early (0.09 to 0.13 sec, average 0.11), and a conspicuous dicrotic wave is found in 75 per cent.

Left Ventricular Puncture

In view of the diagnostic difficulty in selecting suitable cases of aortic stenosis for surgical treatment, left heart catheterization has been used in several centers to measure the pressure gradient across the aortic valve.[2] At the Brompton Hospital this technic has been abandoned in favour of percutaneous left ventricular puncture.[5] A simultaneous or immediately consecutive brachial arteriogram enables the pressure gradient across the aortic valve to be measured with little risk or discomfort to the patient (Fig. 20). These punctures have always been carried out in the operating theatre by a skilled thoracic surgeon, usually Mr. Milstein, so that in the event of ventricular fibrillation immediate cardiac massage, aortic valvotomy, and defibrillation could be undertaken at once. So far, however, the need for this has not arisen, but there was one death from uncontrollable haemorrhage shortly afterward. Necropsy revealed gross occlusive atherosclerosis of the right coronary artery; the apex of the left ventricle was only 3 mm thick, and consisted of little more than loose connective tissue. The puncture wound itself was clean, small, and nicely placed, but penetrated the atrophic zone mentioned. No coronary artery was injured, the aortic valve was sclerotic but not stenosed, and angina was obviously due to coronary disease.

Apart from this tragedy 45 percutaneous left ventricular punctures were remarkably free from complications of any kind. The hypertrophied left ventricle of aortic stenosis may well be a safe-guard against haemorrhage. It is perhaps questionable whether the test should be used for differential diagnosis, as in the fatal case described.

In assessing the degree of aortic stenosis the test was helpful, but far from conclusive. Complete reliance could be placed on it only when the forward stroke flow at the time was known. This was measured by simultaneous cardiac catheterization when there was no aortic incompetence. In the presence of appreciable incompetence, however, the forward stroke flow could not be estimated, and of course it was just in these cases that the chief diagnostic difficulty arose.

Forty-five percutaneous left ventricular punctures and 80 left ventricular punctures immediately before valvotomy provided considerable information concerning the value of the test.

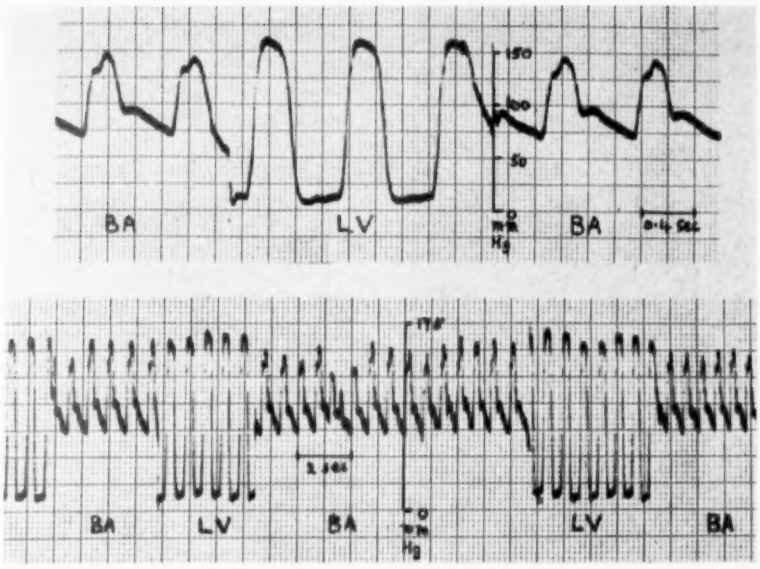

Fig. 20. Immediately consecutive brachial arteriograms and left ventricular pressure pulses in a case of mild aortic stenosis. The gradient is only 15 mm Hg. Note the rapid rate of ascent (1,000 mm Hg/sec) in the brachial arteriogram, and the high anacrotic shoulder.

Since the preoperative findings were mostly similar to those obtained at operation, the two sets of figures may be taken together. They are given here in tabulated form in relation to 87 patients (Table I).

The relatively small gradient in some of the most severe cases was attributed to a reduced stroke flow secondary to heart failure. The small gradient in cases with associated mitral stenosis could be similarly explained. Mitral stenosis also prevents the rise of presystolic left ventricular tension that is so necessary for the left ventricle to generate adequate force to overcome the obstruction.

TABLE I

Data Obtained from Percutaneous (Preoperative) and Direct (Operative) Left Ventricular Puncture

Degree of aortic stenosis	Number of cases	Approximate size of aortic orifice (maximum diameter in mm)	Average l.v.-aortic pressure gradient (mm Hg)	Range of gradient (mm Hg)
Severe (trivial if any, incompetence)	40	Less than 12.5	99	35 to 160
Moderately severe	10	12.5 to 15	96	50 to 200
Relatively mild	5	Over 15	10	0 to 30
Severe, but with appreciable incompetence	8	10 to 12.5	99	50 to 160
Stenosis with dominant incompetence	6	15 to 20	54	10 to 100
Combined aortic and mitral stenosis (both critical)	18	5 to 15	47	20 to 65 (with one of 130)

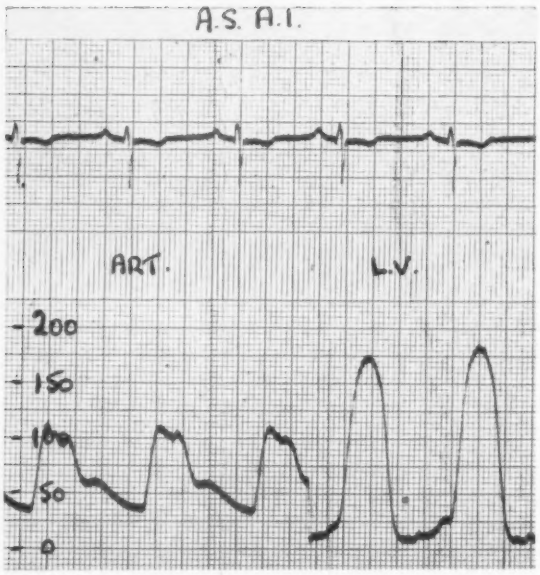

Fig. 21. Immediately consecutive brachial arteriogram and left ventricular pressure pulse in a case of aortic valve disease with dominant incompetence. The gradient is 65 mm Hg. Note the rapid rate of ascent (1,000 mm Hg/sec) in the arteriogram.

The steep gradient in cases with moderate stenosis and significant incompetence (Fig. 21) was attributed to a large forward stroke flow. A high output due to excitement explained the steep gradient in some of the moderate cases.

Cardiac Output: The cardiac output in aortic stenosis is usually well maintained until the onset of heart failure. In 16 cases free from failure the resting output averaged 5.3 *l*/min; in five cases with heart failure, however, it averaged only 3 *l*/min.

Left Atrial Pressure: The giant *a* wave maintaining a high initial left ventricular tension has already been mentioned and illustrated (Fig. 1).

When there is left ventricular failure, however, a giant *v* wave followed by a precipitous *y* descent and deep *y* trough dominates the left atrial pressure pulse (Fig. 22). The *Ry/v* ratio in these cases is consistently very high, averaging 10 and ranging between 4 and 15 in 20 cases in which it was measured. Familiarity with these tracings breeds considerable respect for the diagnostic value of low *Ry/v* ratios in mitral stenosis (Owen and Wood, 1955[19]).

The height of *v* in cases with left ventricular failure averaged 27 mm Hg above the sternal angle, and ranged between 20 and 50 mm Hg. The mean left atrial pressure was usually lower and the end-diastolic pressure higher than in critical mitral stenosis.

Selection of Cases for Valvotomy

Before being in a position to advise valvotomy or otherwise it is necessary to know just what can be expected from the operation and what is the risk. At Brompton 80 cases have been operated on to date, mostly by Sir Russell Brock.[3] These include 19 with associated mitral stenosis which was relieved at the same time.

Results of Surgery

The results, compared with those in 64 cases of similar severity which for one reason or another had to be treated medically, are tabulated in Table II.

TABLE II

Results of Treatment of Aortic Stenosis

	Aortic valvotomy (80 cases) %	Medical treatment (64 cases) %
Mortality		
Immediate	13	—
Remote	7	28 (minimum)
Physiological result		
Excellent	4	0
Good	50	0
Fair or indifferent	16	25 (minimum)
Poor	4	
Badly selected		
Too mild	1	
Too little stenosis and too much incompetence	5	
Summary		
Mortality	20	28+
Good result	54	0
Indifferent result	26	25+

Bailey *et al.*[1] report more or less similar experiences. It follows that symptom-free cases should not be operated on at the present time, for the expected physiological result does not justify the risk.

During the seven-year period in which these

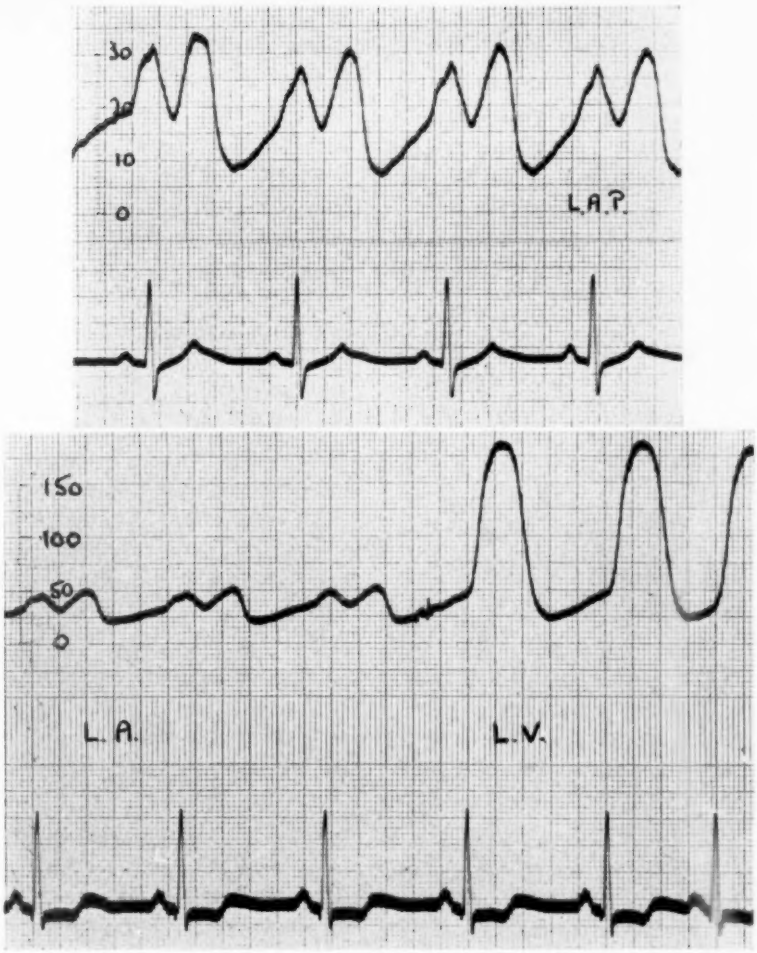

Fig. 22. Left atrial pressure pulse in a case of severe aortic stenosis with left ventricular failure. Note the giant V wave, rapid *y* descent, and deep *y* trough. Left atrial and left ventricular diastolic pressures then rise together.

80 cases have been operated on, there have been 64 comparable cases of severe rheumatic aortic valve disease treated medically; 48 had more or less pure stenosis, and 16 combined stenosis and incompetence; all had symptoms. In the majority, operation was either not advised because of the degree of incompetence, or refused; some of the earlier cases were deferred because of the risk; some died while on the waiting list for operation. Of these 64 cases treated medically, 18 are known to have died of their diseases, giving a minimum mortality of 28 per cent over the period under review. Since half the medically treated cases have not been followed up at our clinic, the mortality could well be double this figure. Although angina pectoris and heart failure may have been kept under control or relieved by medical means, it would be foolish to claim that any of these medically treated cases had improved sufficiently to be classified as good results; the best would be classed as fair or indifferent by the standards applied to surgical cases. These figures leave no doubt that serious cases of aortic stenosis with symptoms should be offered surgical treatment.

STANDARDS OF IMPROVEMENT

It may help to define the standards of improvement adopted.

Excellent means virtual abolition of the pressure gradient across the aortic valve (Fig. 23), restoration of the wave form of the brachial pulse to normal (Fig. 24), and abolition of all symptoms during ordinary day to day activity after the patient has resumed his occupation.

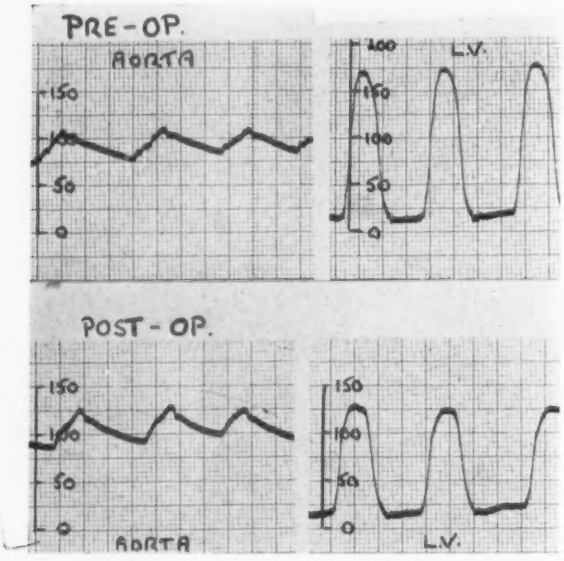

Fig. 23. Central aortic and left ventricular pressure pulses before and after successful aortic valvotomy. Note the abolition of the gradient.

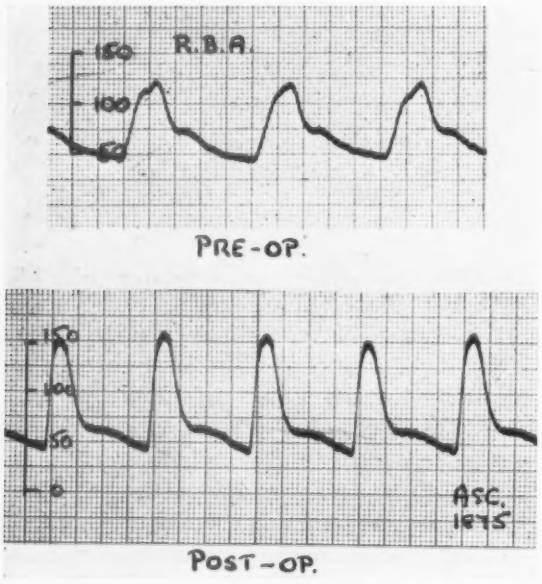

Fig. 24. Brachial arteriograms before and after successful aortic valvotomy. The rate of ascent has increased from 415 to 1,875 mm Hg/sec, the anacrotic shoulder has risen to merge with the summit, maximum pressure is reached much earlier and ejection is no longer delayed.

Good means reducing the pressure gradient to about half (without raising the left ventricular diastolic pressure), raising the central aortic pressure and the height of the anacrotic notch, improving the form of the brachial arteriogram, and improving effort tolerance by two grades; effort syncope should be abolished, angina abolished or greatly reduced, and heart failure objectively relieved.

Fair or indifferent means reduction of the gradient by no more than one third, only slightly raising the height of the anacrotic notch, and failing to alter the form of the brachial pulse appreciably, whatever the patient may say about his symptoms. Not infrequently the symptoms are temporarily improved, but reappear when the psychological effect of the operation has worn off.

Poor means failure to alter the gradient, or altering it only by reducing the stroke output of the left ventricle (aortic pressure lower and left ventricular diastolic pressure higher); failure to alter the central aortic pressure pulse and the brachial arteriogram; failure to achieve a palpable split or producing obvious severe aortic incompetence; and as a rule, failure to relieve symptoms, although the patient may again claim improvement for psychological reasons. Heart failure may prove very troublesome and difficult to control during the immediate postoperative period in these cases.

INDICATIONS FOR VALVOTOMY

The following criteria provide sound grounds for advising aortic valvotomy in suitable clinics:

(1) Angina pectoris or effort syncope (both with 10 per cent exceptions).

(2) Left ventricular failure or congestive heart failure. The risk may be heavy in these cases, but it is far from prohibitive, and the medical outlook is hopeless.

(3) A small anacrotic pulse of low pressure.

(4) Invisible carotid pulsation.

(5) A hypertrophied rather than grossly dilated left ventricle.

(6) Absence of an obvious aortic ejection click (25 per cent exceptions).

(7) Delayed aortic valve closure resulting in a single or paradoxically split second heart sound in the absence of left bundle branch block or serious aortic incompetence.

(8) Absence of a loud aortic diastolic murmur (10 per cent exceptions).

(9) An electrocardiogram showing considerable left ventricular preponderance or left bundle branch block.

(10) An x-ray film revealing an inconspicuous aortic knuckle, with or without post-stenotic dilatation of the ascending aorta, and hypertrophy rather than dilatation of the left ventricle (except in cases with left ventricular failure).

(11) A direct arteriogram exhibiting a slow initial upstroke (200 to 700 mm Hg per sec), depressed anacrotic shoulder or notch, delayed maximum pressure or tidal peak (0.20–0.28 sec when corrected for rate by dividing by the square root of the cycle length), and small pulse pressure (30–50 mm Hg).

(12) A pressure gradient across the aortic valve above 50 mm Hg with relatively pure stenosis, above 25 mm Hg when there is associated mitral stenosis or congestive heart failure, and above 100 mm Hg when there is appreciable incompetence.

(13) An aortic valve orifice measuring less than 0.75 cm^2 according to the Gorlin formula.

CONTRAINDICATIONS TO VALVOTOMY

The chief contraindications may be listed as follows:

(1) Age over 65 years.

(2) Absence of symptoms.

(3) A full, waterhammer, obviously bisferiens, or high tension pulse.

(4) A brachial systolic blood pressure over 170 mm Hg at rest, or a pulse pressure over 70 mm Hg.

(5) Conspicuous carotid pulsation.

(6) A hyperkinetic dilated left ventricle.

(7) A normally split second heart sound, A_2 falling before P_2.

(8) An exceptionally loud aortic diastolic murmur.

(9) A normal electrocardiogram (or one showing evidence of cardiac infarction).

(10) An unduly prominent aortic knuckle, conspicuous descending aorta, or grossly dilated left ventricle (in the absence of heart failure).

(11) A direct arteriogram showing a rapid initial upstroke (over 700 mm Hg per sec), or early "tidal" peak (under 0.16 sec when corrected for rate).

(12) An inadequate pressure gradient across the aortic valve for the type of case being investigated (see positive criteria).

(13) A valve orifice calculated to exceed 0.75 cm^2.

SUMMARY

(1) A series of 250 cases of aortic stenosis has been analysed; 196 were rheumatic and 54 congenital.

(2) Aortic valve disease is half as common as mitral valve disease, and aortic stenosis twice as common as pure aortic incompetence.

(3) The symptoms of severe aortic stenosis, when present, are angina pectoris (70 per cent), effort syncope (33 per cent), and those of left ventricular failure (45 per cent) or congestive heart failure (15 per cent).

(4) The most important physical signs of severe aortic stenosis are a small prolonged anacrotic pulse of low tension, invisible carotid pulsation, and a hyperdynamic rather than hyperkinetic cardiac impulse.

(5) An aortic systolic murmur at apex or base is invariable in aortic stenosis; in the absence of incompetence and heart failure its length is related to the degree of stenosis.

(6) In the presence of aortic incompetence, neither an aortic systolic thrill nor reversed splitting of the second heart sound indicate dominant stenosis; only in the absence of incompetence are those two signs related to the degree of obstruction, and the thrill may disappear with the onset of heart failure.

(7) The aortic ejection click bears an inverse relationship to the degree of stenosis.

(8) Absence of the aortic second sound is rare in aortic stenosis, and when so recorded usually implies ignorance of modern auscultatory techniques and nomenclature.

(9) A soft or moderate aortic diastolic murmur proves little beyond the presence of aortic valve disease; its presence in a case of congenital stenosis does not even determine the site of

the stricture—whether valvular or subvalvular. Only a loud aortic diastolic murmur favours dominant incompetence.

(10) The electrocardiogram is normal in all mild and most moderate cases, but is never normal in severe cases; in these considerable left ventricular preponderance with secondary T wave inversion is found in 80 per cent and left bundle branch block in 14 per cent.

(11) Atrial fibrillation occurred in 13 per cent of the rheumatic cases, all of which had associated mitral valve disease. It did not occur in any of the congenital cases.

(12) The classic radiologic changes of aortic stenosis include a small aortic knuckle, poststenotic dilatation of the ascending aorta, valve calcification in 80 per cent of cases over 30 years old, and hypertrophy rather than dilatation of the left ventricle (in the absence of heart failure).

(13) The direct brachial arteriogram in severe stenosis shows a relatively small pulse pressure (30 to 50 mm Hg), slow initial rate of ascent from onset to anacrotic shoulder (200 to 700 mm Hg per sec; average 450), low anacrotic shoulder (50 to 75 per cent of maximum pressure), delayed maximum pressure or tidal wave (usually 0.20 to 0.28 sec after the onset when corrected for rate), relatively low maximum pressure (90 to 170 mm Hg; average 120), delayed dicrotic notch (0.34 to 0.40 sec after the onset when corrected for rate; average 0.37 sec), and absence of a positive dicrotic wave.

(14) Dominant aortic incompetence with relatively mild stenosis alters this tracing chiefly by increasing the pulse pressure (average 72 mm Hg), increasing the speed of the first ascent (usually 700 to 1,000 mm Hg per second; average 850), raising the level of the anacrotic shoulder to about 80 per cent of maximum pressure (range 66 to 100 per cent), changing the shape of the anacrotic shoulder to a flat, more prolonged plateau or depression (pulsus bisferiens), and increasing the maximum pressure which may be either the "percussion" or "tidal" waves; but both the tidal wave and the dicrotic notch remain delayed.

(15) The two chief variations of the aortic stenotic pulse are caused by (a) an unusually low and ill-defined anacrotic shoulder, and (b) dwarfing or disappearance of the "tidal" wave resulting from an exceptionally small forward stroke flow.

(16) The central aortic pressure pulse differs chiefly in the situation of the anacrotic notch, which in severe cases is very low (10 to 33 per cent of maximum pressure). In addition, the tidal wave is more delayed and the dicrotic notch appears higher on the descending limb.

(17) The maximum systolic pressure gradient across the aortic valve varies directly with the degree of stenosis and the forward stroke flow. The range in severe cases is 30 to 200 or more mm Hg, being lowest when there is associated mitral valve disease or heart failure, and highest when a good output is maintained. When there is dominant aortic incompetence and relatively mild stenosis gradients range between 10 and 100 mm Hg (average 54).

(18) The resulting cardiac output averaged 5.3 *l*/min in 16 cases of severe stenosis free from heart failure, and 3 *l*/min in 5 cases in failure. Outputs exceeding 7 *l*/min were encountered only in relatively mild cases.

(19) The left atrial pressure pulse in severe aortic stenosis is characterized by giant *a* waves in most cases free from failure, and by giant *v* waves averaging 27 mm Hg above the sternal angle (range 20 to 50), followed by steep *y* descents and deep *y* troughs in those with failure. The *Ry*/*v* ratio averaged 10 (range 4 to 15). In cases with failure the mean left atrial pressure was usually lower, and the end-diastolic pressure higher than in critical mitral stenosis.

(20) The results of aortic valvotomy in 80 cases are described and compared with those obtained in 64 cases of similar severity treated medically. Surgically, the immediate and remote mortality was 20 per cent, whereas medically it was well over 30 per cent; surgically good results were obtained in 54 per cent, an achievement quite impossible by medical means.

Conclusion

In conclusion, one might say that at the present time aortic valvotomy is too hazardous

and too crude an operation to advise when it is most desirable (just before the onset of symptoms), and frequently too late when impending disaster makes it imperative; nevertheless, the results of skilled surgical treatment far outweigh anything that medicine has to offer.

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Left Ventricular, Central Aortic, and Peripheral Pressure Pulses in Aortic Stenosis*

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NUMEROUS attempts have been made to estimate the degree of aortic stenosis by inspection of the peripheral and central aortic pressure pulses.[1–3] Katz and associates[1] have shown experimentally that the position of the anacrotic notch was related to the degree of constriction of the aorta in animals. Goldberg and associates[2] have shown that the position of the anacrotic notch is a function of the pulse pressure or stroke volume as well as the degree of aortic obstruction. Recently, Duchosal and associates[3] have attempted to estimate the degree of obstruction by the use of carotid artery tracings.

With the introduction of left heart catheterization,[4,5] accurate measurements of the pressure gradient across a stenotic valve could be obtained. Simultaneous catheterization of the right and left heart has allowed for measurements of the pressure-flow relationships and estimation of the orifice size in patients with aortic stenosis.[6–8] This has provided a method for quantitating the amount of obstruction at the valve and has given opportunity for a more accurate evaluation of the central and peripheral arterial pressure pulses in man.

MATERIALS AND METHODS

Simultaneous catheterization of the right and left heart was performed in 19 patients, in whom the diagnosis of "pure" aortic stenosis was confirmed at surgery.

Right heart catheterization was performed in the usual manner, except that the patient was in the prone position. Left atrial puncture was done by employing a 6″ #18G thin walled needle as described previously.[5] A polyethylene or nylon catheter was inserted through the needle. With continuous monitoring of the pressure by a capacitance type manometer recording on a direct writing polyoscillograph (Sanborn), or in some cases strain gauge manometers with recording by photo-oscillographic technic,† the catheter was advanced until the tip lay in the left ventricle or aorta. The cardiac output was obtained by the direct Fick method. Pressures were then simultaneously recorded from the left ventricle, brachial artery, and/or aorta.

In those cases where the brachial artery, aorta, and left ventricle were not superimposed by the recording method employed, this was accomplished by means of the simultaneously recorded electrocardiogram with due allowance for pulse transmission time. The systolic pressure gradient was measured by planimetric integration and the estimation of aortic valve area was calculated by a modification of the formula of Gorlin and Gorlin.[9]

For clinical purposes it has been found that the brachial artery pressure pulse tracings may be substituted for those of the aorta in the measurement of the aortic systolic pressure gradient and valve area.[8]

In order to express the position of the anacrotic notch with respect to the peak of systolic pressure, the distance in centimeters from the end-diastolic pressure to the anacrotic notch was

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measured and designated as X. The distance from the end-diastolic pressure to the peak of systole was designated as Y. The percentage was then calculated from the expression: [X/Y × 100].

Results

The complete hemodynamic data of these patients will be presented elsewhere.[10]

Brachial Artery and Aortic Pressures: The systolic pressure of the brachial artery ranged from 96 to 140 mm Hg. The central aortic pressure was measured simultaneously with that of the brachial artery on thirteen occasions. The systolic pressure of the aorta ranged between 78 and 136 mm Hg. The systolic pressure of the brachial artery exceeded that of the aorta in all but one case, in which it was the same.

The diastolic pressure of the brachial artery ranged between 60 and 100 mm Hg. In the simultaneously measured central aortic tracings, the diastolic pressure ranged from 50 to 98 mm Hg. The diastolic pressures were the same in two patients, higher in the central aorta in five, and lower in six cases.

The pulse pressure of the brachial artery ranged from 24 to 68 mm Hg and that of the central aorta from 12 to 56 mm Hg. The pulse pressure of the brachial artery exceeded that of the more central tracing in all cases but two.

The time from the onset of the brachial artery pressure pulse to the peak of systole varied between 0.09 and 0.26 sec. It was greater than the upper limits of normal[2] of 0.12 sec in all but two patients in which this value was 0.09 and 0.10, respectively.

In three patients there was a double hump at the crest of the brachial artery pressure pulse; the second and slightly higher of these two was taken to correspond to the peak of systole. The time to this point in these three patients was 0.14, 0.18, and 0.16 sec.

In the central aorta tracing, the time from the onset to the peak of systole ranged from 0.12 to 0.28 sec. This time interval was more prolonged in the central aortic than in the brachial artery tracing in all cases but four. Of the latter, this time interval was the same in two and shorter in the aorta in the remaining two cases.

Anacrotic Notch: A distinct anacrotic notch or slur was observed in the brachial artery pressure tracing of 13 patients. Of the six patients in whom there was no anacrotic notch, three had a double hump at the peak of systole, two had some flattening after the peak on the dicrotic side and one had a normal contour.

In those patients in whom an anacrotic notch or slur was observed in the brachial artery tracing, its time from the onset of the pulse varied from 0.06 to 0.16 sec.

A distinct anacrotic notch was observed in the central arterial tracing in all patients. The time of its occurrence from the onset of the pressure pulse ranged from 0.02 to 0.08 sec.

The anacrotic notch occurred earlier in the central aorta than in the brachial artery in all cases but one where it was the same. This was true even in those tracings with the double hump at the systolic crest if the first hump was interpreted to be a reflection of the anacrotic notch.

In those patients in whom there was an anacrotic notch on the brachial arterial tracing, and not including the three patients in whom there was a double peak, the height of the anacrotic notch [X/Y × 100] was 54–89 per cent of the pressure pulse. In those patients in whom there was an anacrotic notch in the central aortic tracing, the anacrotic notch was lower in all instances—the [X/Y × 100] being 17 to 67 per cent. In general, the contour of the brachial artery was smoother and more peaked than that of the central aorta.

Ventricular Output and Pressures: The cardiac output was reduced in the group as a whole, averaging 3.7 and ranging from 2.6 to 5.6 *l*/min. The stroke volume varied from 25 to 66 cc/beat. Although there was wide variation in the aortic valve flow, the latter was low for the group as a whole, ranging from 100 to 232 cc/systolic ejection seconds. The functional orifice size of the aortic valve was reduced, ranging from 0.3 to 0.9 cm^2.

The systolic pressure of the left ventricle varied from 150 to 232 mm Hg and the diastolic from 7 to 26 mm Hg. The isometric contraction period was prolonged in the majority of cases, ranging from 0.04 to 0.09 sec.

The contour of the curves of the left ventricle

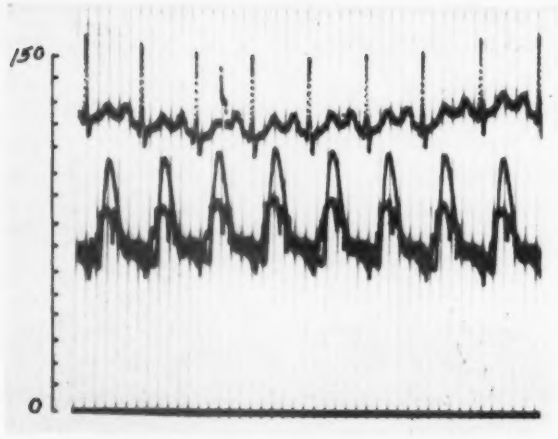

Fig. 1. Simultaneously recorded brachial artery (smooth curve) and aortic (multiple artifacts) pressure pulses in a patient with a normal aortic valve. Note earlier yet higher peak of brachial artery pressure pulse. Time lines 0.1 sec. ECG above.

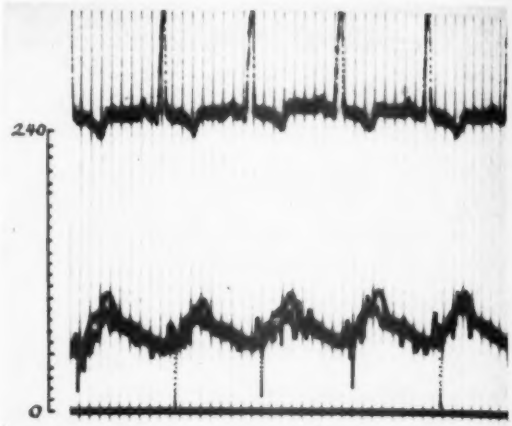

Fig. 2. Simultaneously recorded brachial artery (smooth curve) and aortic (multiple artifacts) pressure pulses in a patient with aortic stenosis. Note the contours of the brachial artery and aortic curves more closely resemble one another than in the normal, although the aorta shows increase in the number of artifacts. Time lines 0.1 sec. ECG above.

and aorta did not resemble one another during systole. In all cases, the peak of the aortic curve appeared slightly later than that of the left ventricle.

In all cases the pressure pulse of the left ventricle showed a rapid rise to a smooth rounded peak and a slower decline after the dicrotic incisura. The systolic ejection period was generally prolonged, ranging from 0.23 to 0.34 sec. There was no correlation between the duration of the systolic ejection period and the heart rate.

Pulsus Alternans: An interesting observation was the frequent occurrence of a mechanical pulsus alternans in the left ventricle, aortic, or brachial artery pressure pulses. This was characterized by regular variations in pulse pressure without change in length of the cardiac cycle or electrocardiogram. This phenomenon occurred in 8 or 42 per cent of the patients in this series. It was found to occur only in the systemic circulation in all cases.

Discussion

It has long been known that as the arterial pressure pulse proceeds to the periphery, there are changes in both magnitude and contour. The peripheral pulse exhibits a more rapid ascent to an earlier, yet higher, peak. The diastolic pressure falls slightly as it is transmitted from the central aorta. Thus the peripheral pulse pressure is increased over that of the more central pulse (Fig. 1).

Normally in animals there is a small vibration on the anacrotus of the aortic pulse which is not transmitted to the periphery.[11] This is also seen in human subjects as demonstrated by Fig. 1. However, in aortic stenosis, where there is a decrease in the violence of systolic discharge, standing waves are not set up. The intermediate and peripheral pulses more closely resemble the central pulse[12] (Fig. 2). The increased turbulence in aortic stenosis is expressed by the multiple vibrations seen on the aortic pressure pulse, and these are felt to be the anlage of the anacrotic notch in the peripheral pulse[13] (Fig. 2).

In the experimental animal during constriction of the aorta it has been shown that the contour of the aortic and left ventricular pressure pulses do not resemble one another during the time of systolic ejection and these changes are thought to be due to loss of energy across a stenotic valve and increased diastolic size.[1] The left ventricular pulse is higher than that of the aorta, rising to peaked summit, and with a steep descent. Thus in aortic stenosis the left ventricle contracts more "isometrically." Also, in this condition the peak of the aortic pressure pulse is reached markedly later than the peak

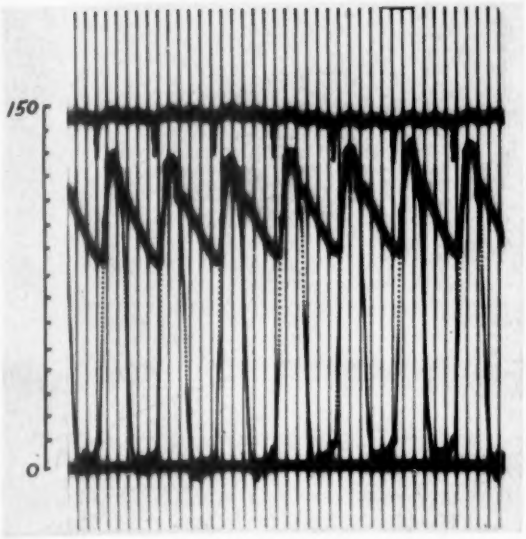

Fig. 3A. Left ventricular and aortic pressure pulses simultaneously recorded in a patient with a normal aortic valve. Time lines 0.1 sec. ECG above.

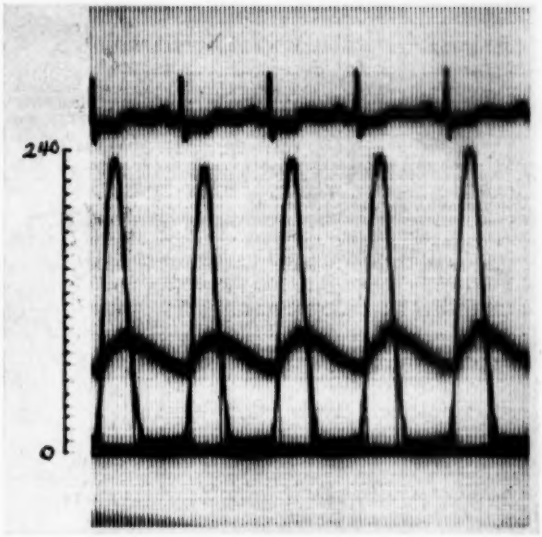

Fig. 3B. Left ventricular and aortic pressure pulses simultaneously recorded in a patient with aortic stenosis. Note differences in height of two curves. Peak of aortic curves occurs later than that of the left ventricle. Left ventricular curve is more peaked and with steeper descent than in normal. Time lines 0.04 sec. ECG above.

of the left ventricular pressure pulse (Fig. 3, A and B).

The end-diastolic pressure in the left ventricle was elevated in the majority of cases. This could be explained in some cases by left ventricular failure. There was generally no correlation between the level of the diastolic pressure and clinical failure of the left ventricle. It is felt that in addition to failure, elevation of the diastolic pressure in these individuals is due to alteration in the pressure-volume elasticity relationships secondary to hypertrophy.

Attempts have been made to correlate the position of the anacrotic notch with the degree of obstruction. Katz and associates[1] have shown experimentally that with increasing constriction of the aorta just distal to the aortic valve, the amplitude of the peripheral pulse was reduced and the anacrotic notch moved to a lower position on the ascending limb. This preparation, however, bears little resemblance to rheumatic valvular aortic stenosis, as the position of the ligature undoubtedly raised the diastolic pressure of the aorta near the origin of the coronary arteries, thus increasing flow to the myocardium.

The influence of the stroke volume or pulse pressure as well as the degree of obstruction was suggested by Goldberg and associates[2] who noted the changes in contour of the brachial arterial tracing in the poststraining period of the Valsalva maneuver and in patients with auricular fibrillation. Other factors to be considered which may influence the contour of the arterial tracing in the normal heart are changes in the state of the myocardium and peripheral resistance,[14] elasticity of the arterial tree[15] and velocity of ejection.[16]

Although many explanations have been advanced to explain the position of the anacrotic notch, it appears that multiple factors must be considered and no single event can be considered as predominant. Indeed Figures 4A, B, C, and D show there is no demonstrable relationship between the position of the anacrotic notch in either the aortic or brachial artery pressure pulse and the stroke volume, pulse pressure, systolic pressure gradient and calculated aortic valve area. There was a similar lack of relationship between the time to the peak of systole and stroke volume, pulse pressure, systolic pressure gradient, and aortic valve area. Furthermore, Figure 5 shows the brachial artery tracings of four patients with various degrees of

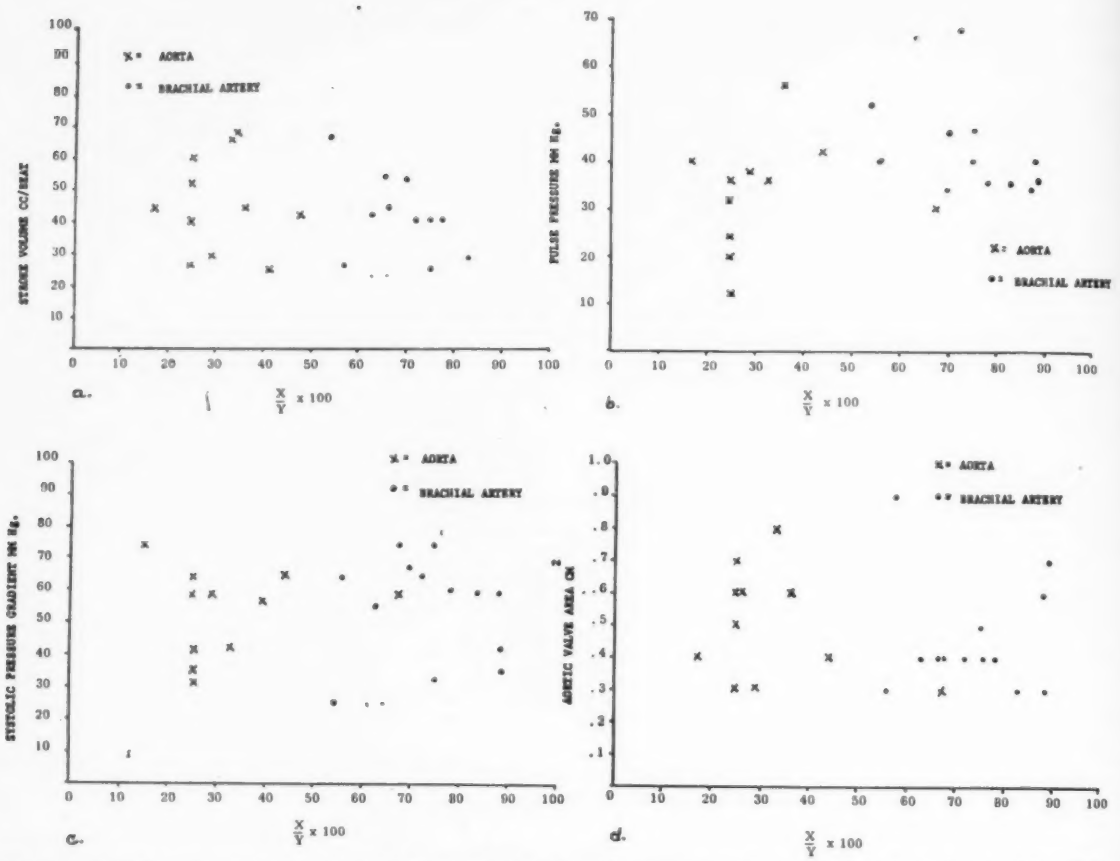

Fig. 4. Position of anacrotic notch [X/Y × 100] in brachial artery and aorta plotted against: (a), stroke volume; (b), pulse pressure; (c), systolic pressure gradient; (d), aortic valve area. Note lack of correlation.

aortic stenosis. The positions of the anacrotic notch, although moving to a lower position on the ascending limb, in no way accurately reflect the degree of obstruction at the valve.

Although the anacrotic notch usually is seen in aortic stenosis, its presence is not pathognomic of this disease. Many patients with surgically proved pure mitral stenosis have a distinct anacrotic notch in the brachial artery tracing, despite the lack of a systolic pressure gradient across the aortic valve during left heart catheterization. These were not felt to be artifacts introduced by the position of the indwelling needle, or to impedance in the manometric system. An anacrotic notch on the peripheral artery tracing may likewise be found in many other abnormal conditions, such as patent ductus arteriosus and coarctation of the aorta. Two patients studied in this laboratory with normal cardiovascular systems have shown anacrotic notches in their peripheral arterial tracings with a delay to the peak of systole. Conversely, one patient of this group with aortic stenosis had a normal peripheral pressure pulse (Fig. 5, top).

The mechanical pulsus alternans, which was found to occur only in the systemic circulation in 48 per cent of our patients, demonstrated the unilateral pulsus alternans recently described by Ferrer and associates[17] (Fig. 6). In their group of 21 patients exhibiting pulsus alternans, six were shown to have this phenomenon in the systemic circulation only. Only one of these six, however, had aortic stenosis. In their study, as in ours, there was no change in the end-diastolic pressure of the left ventricle, aorta, or brachial artery, nor was it felt to be influenced by respiration. The explanation of this offered by Wiggers[18] was that there were periodic changes in the state of the myocardium. However, Ferrer

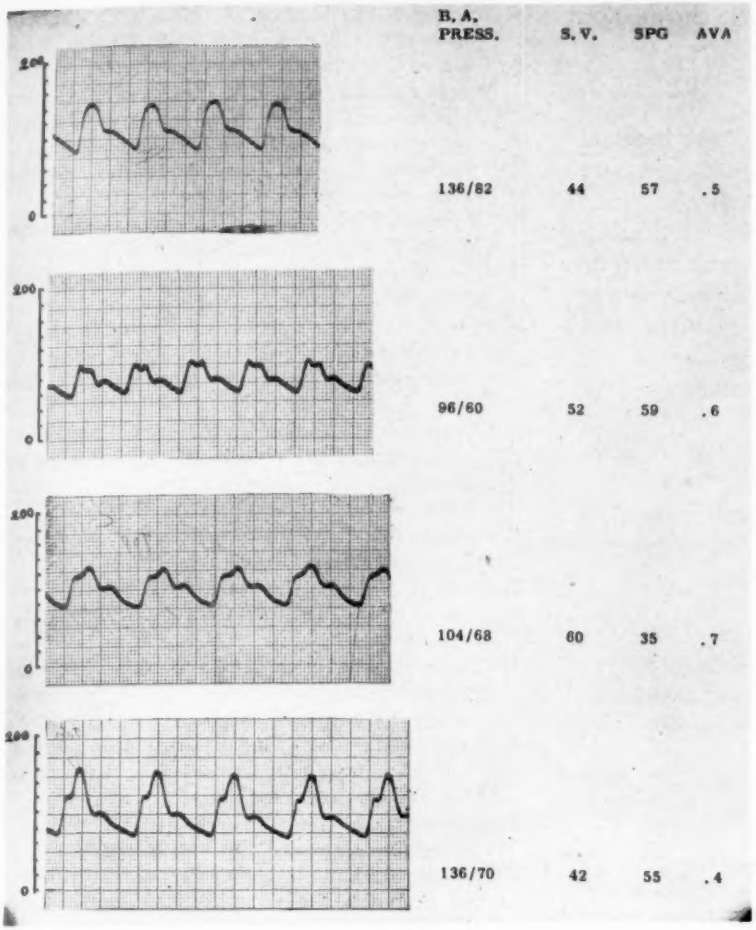

Fig. 5. Brachial artery pressure tracings in four patients with various degrees of aortic stenosis. Note position of notch does not reflect degree of obstruction. B.A. pres. = brachial artery pressure; S.V. = stroke volume; S.P.G. = systolic pressure gradient; A.V.A. = aortic valve area.

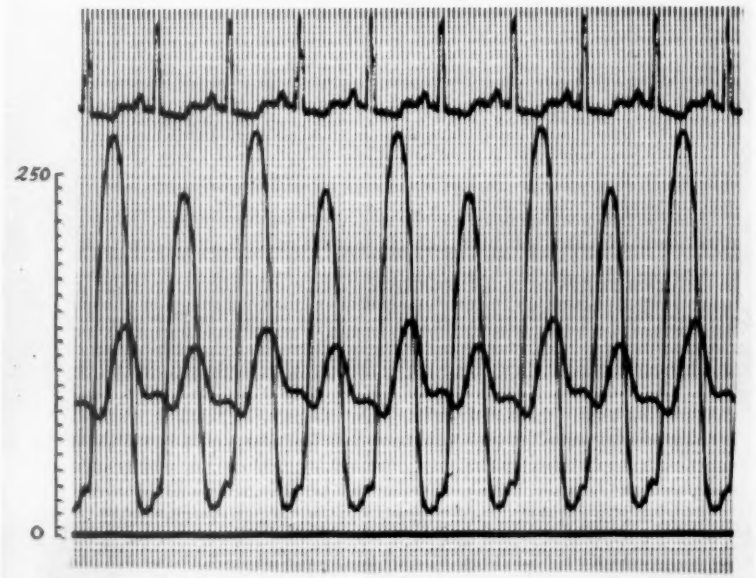

Fig. 6. Left ventricular and brachial artery tracings superimposed showing mechanical pulsus alternans. ECG above.

and associates could offer no single explanation of its occurrence.[17]

Summary

(1) Changes in the contour of the brachial artery, left ventricular, and aortic pressure pulses in aortic stenosis are discussed.

(2) There is no demonstrable relationship between the position of the anacrotic notch or its time of occurrence and the stroke volume, pulse pressure, systolic pressure gradient, and aortic valve area. Thus the position of the anacrotic notch is no index of the degree of aortic stenosis.

(3) Factors influencing contour of the arterial pressure pulse are discussed.

(4) A high incidence of unilateral mechanical pulsus alternans is noted in the left ventricular and brachial artery pressure pulses.

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Further Studies on Coronary Sinus Rhythm*

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WHILE OTHER forms of A-V rhythm—so-called upper, middle, or lower A-V rhythm—are rare, coronary sinus rhythm is relatively common. In this disturbance the P waves show the characteristic form of an A-V rhythm but the P-R interval is within normal limits and approximately the same as that of the sinus rhythm of the patient. The P waves are low positive in lead I and deeply inverted and often peaked in leads II and III; furthermore it is characteristic that the P waves are positive in lead aVR and negative in lead aVF. This rhythm originates in the extension of the A-V node toward the area of the orifice of the coronary sinus vein, an area which has a high degree of automatism. In the normal dog heart increasing the automaticity of the specialized fibers by warming this area leads to replacement of the normal sinus rhythm by coronary sinus rhythm.[3,6]

This form of A-V rhythm is very labile. Changes of posture, inhalation of amyl nitrite, carotid pressure or an intervening extrasystole may elicit it or change it into sinus rhythm. Figure 1 shows, in an experiment on a dog, how sinus rhythm is temporarily replaced by coronary sinus rhythm after induction shocks caused a series of rapid atrial extrasystoles.

The rate of impulse formation in the A-V node is only slightly less than in the sinus node, the difference often amounting only to 10 to 15 beats per minute and sometimes even less. Therefore, a slight slowing of one rhythm brings the other one out and continuous interferences of both rhythms are common. It is not as yet clear why coronary sinus rhythm does not appear regularly either in man or experimentally when sinus node activity is depressed. In the dog clamping the sinus node more often causes A-V rhythm with simultaneous excitation of atria and ventricles than coronary sinus rhythm. Since the extension of the A-V node to the coronary sinus area is more readily inhibited by the vagus than the rest of the A-V

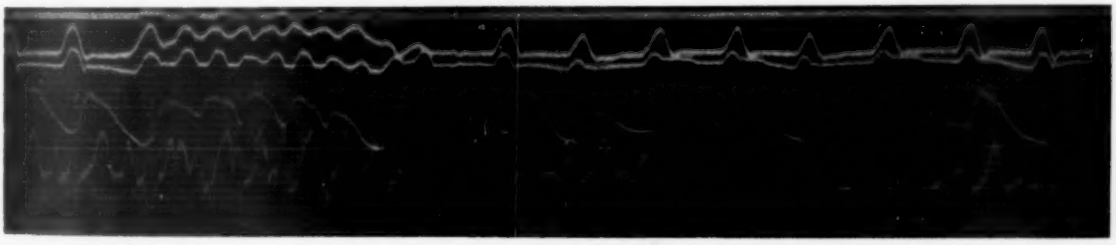

Fig. 1. Dog experiment, with the heart exposed. The top tracing is a signal indicating stimulation with induction shocks. The next three tracings are mechanical ones, representing the contractions of the right and left atria and of the right ventricle. Then, one sees the electrocardiogram and finally the time marker ($^1/_{50}$ of a second). After three normal sinus beats the right atrium was stimulated electrically. Some of the atrial extra beats are aberrantly conducted to the ventricles. After the end of the stimulation two atrial extrasystoles appear as an after-effect. They are followed by a series of six beats originating in the coronary sinus area; the P waves are deeply inverted. The lead is from anus and esophagus corresponding roughly to lead 3. Finally, sinus rhythm returns.
Note that the P-R interval is virtually the same with both rhythms. It is typical that during the coronary sinus rhythm the left atrium contracts slighly before the right one, while the reverse is true during sinus rhythm.

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node, it is possible that any sudden increase of vagus tonus inhibits the coronary sinus while the rest of the A-V node is not affected. This would explain the frequent experimental observation that inhibition of sinus node activity by rougher methods, such as clamping, leads to the appearance of an A-V rhythm originating in the lower portion of the node while more gentle inhibition of sinus node activity leads to coronary sinus rhythm.

The differentiation from upper A-V rhythm is easy as this rhythm may be assumed to exist if the characteristic P wave pattern described above is present with a P-R interval of less than 0.12 sec. The differential diagnosis is more difficult if the P-R interval is 0.12 sec or more and comparison with normal sinus beats is not possible so that the length of the normal P-R interval cannot be established.

MECHANISM OF PRODUCTION

Three mechanisms may lead to A-V rhythm. If the rate is rapid, one may assume that an abnormality in the A-V node causes it to form impulses faster than the sinus node. This may be due to two factors: (a) a simple acceleration caused by local metabolic processes or other mechanisms leading to faster depolarization of the specialized fibers in this area; (b) an actual paroxysmal tachycardia due to an ectopic abnormal impulse formation. This latter possibility is not common but is often diagnosed when actually a simple atrial tachycardia is present. In the latter the P waves are often hidden in the preceding T or QRS complex.

A second form of A-V rhythm is common, that having the same rate as the previous sinus rate. In such cases it may be assumed that the A-V rhythm appears because the effect of vagal inhibition is greater on the fibers of the sinus node than on the A-V node or possibly because the sympathetic nerves accelerate the fibers of the A-V node more than those of the sinus node. In our opinion most of the A-V rhythms depicted in this paper belong to this group.

In the third form the rate of the A-V rhythm is slow. In such cases the sinus node has ceased to work or is so slow that the A-V centers are able to escape. This form is seen in complete sinus block or when a pathologic process in the area of the sinus node has depressed it abnormally. The most common cause is an occlusion of the artery supplying the sinus node. It is interesting to note that this form of coronary sinus rhythm is rare if indeed it exists at all. When the pacemaker shifts to the A-V node it is in the upper, middle, or lower part of the node that it originates.

DIFFERENTIATION OF TYPES OF A-V RHYTHM

A differentiation between these three main forms is usually but not always possible. It is of practical value as in some of these a pathologic process is responsible while in others it is functional, due to a simple variation of the normal mechanism.

Two factors would appear to be of importance in the differentiation of these rhythms, namely, the rate and the mode of onset and termination. In the following discussion these factors will be evaluated.

The Factor of Rate: The differentiation based mainly on the rate often leads to errors. Sinus bradycardia due to a high vagal tone leads to a similar slowing of the fibers of the A-V node and therefore such a slow sinus rate will not be likely to be replaced by an A-V rhythm. In the bradycardia commonly seen in athletes, A-V rhythm is rare, because there is a strong influence of the vagal tone on the A-V node as proved by the P-R interval which is often 0.24 sec or more.

It is an established fact that the automaticity of the secondary and tertiary centers diminishes progressively as the pacemaker moves down from the sinus to the ventricles. However, abnormal ectopic rhythms elicited mechanically or chemically in the deeper centers often have exactly or almost exactly the same rate as the preceding sinus rhythm.[4,5] This is seen in the course of cardiac catheterization when mechanical irritation of the endocardium near the bases of the ventricles leads to ectopic ventricular rhythms at the rate equal to that of the preceding sinus rhythm. In such cases it may occur that fortuitously the ectopic beats are preceded by normal P waves at a short P-R interval. Such beats have repeatedly been attributed erroneously to the pre-excitation syndrome.[4]

Thus, the ectopic rhythm may be of abnormal

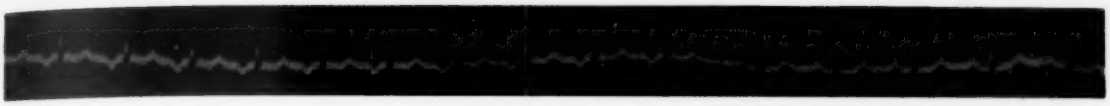

Fig. 2. Spontaneous transition of coronary sinus rhythm into normal sinus rhythm. Note the pause after the end of the coronary sinus rhythm.

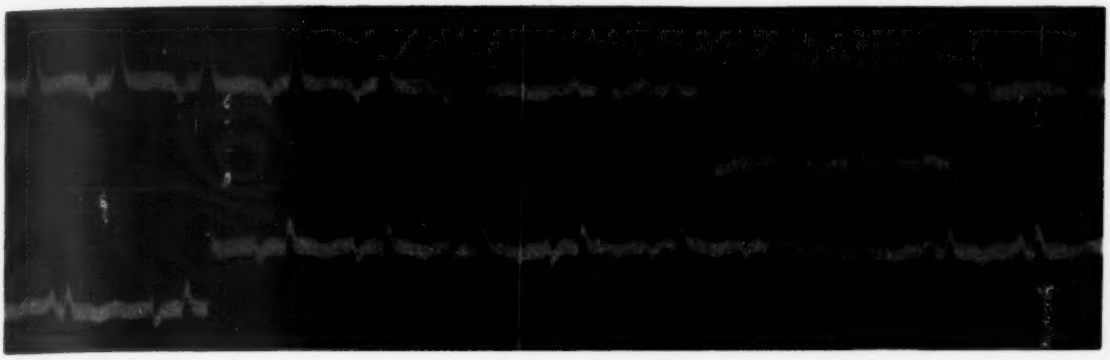

Fig. 3. Sudden end of a coronary sinus rhythm in a 46-year-old woman with an anterior wall infarction (upper tracing, lead 3). The lower tracing (lead V_1) shows the end and the beginning of coronary sinus rhythm. While the end is sudden and followed by a pause (after first beat), the beginning is gradual (near end of strip).

origin but the rate is the same as that of the sinus rhythm. Consequently one is not justified in assuming that when the A-V rhythm or the rhythm originating in the coronary sinus area has the same rate as the sinus node one is dealing with a harmless interference of the two centers. It may well be due to a pathologic process in the A-V node.

Mode of Onset and Termination: A second feature which is said to be of value in the differentiation of a physiologic activity of the A-V node and an abnormal "heterogenetic," ectopic A-V rhythm is the mode of onset and termination of the arrhythmia. Theoretically it would seem that if the new rhythm is due simply to an increase in automaticity, variation of nerve tonus, etc., one rhythm should change gradually into the other leading to periods of interference of the two rhythms. As in parasystole this interference should lead to the appearance of combination beats of the P waves, that is, intermediary P waves combining the features of both centers when the activation of the atria is almost simultaneous. On the other hand a heterogenetic rhythm should start suddenly, early in diastole, should have a constant coupling and should be followed by a "post-extrasystolic" pause. However these theoretic differences do not hold true practically.

Clinical Observations

We studied 28 instances of coronary sinus rhythm. Nine of these showed a constant abnormal rhythm during the whole period of observation and therefore it was not possible to study the mode of onset or termination in these cases. In seven instances the change from one rhythm to another was always gradual and in 12 instances the onset and termination was sudden. The striking feature was that in the same patient the onset could be gradual and the end sudden and followed by a pause; in other cases both the beginning and the end could be sudden one day and gradual on the next.

Figure 2 was obtained from the same patient as Figure 3 in a previous study of coronary sinus rhythm.[6] While often the end of the coronary sinus rhythm and the re-establishment of sinus rhythm occurred gradually, Figure 2 shows a sudden termination followed by a long pause. The transition from one rhythm to the other was spontaneous.

Figure 3 shows the sudden end of a fast A-V rhythm followed by a pause. However, the rate of the sinus rhythm is identical and the onset of

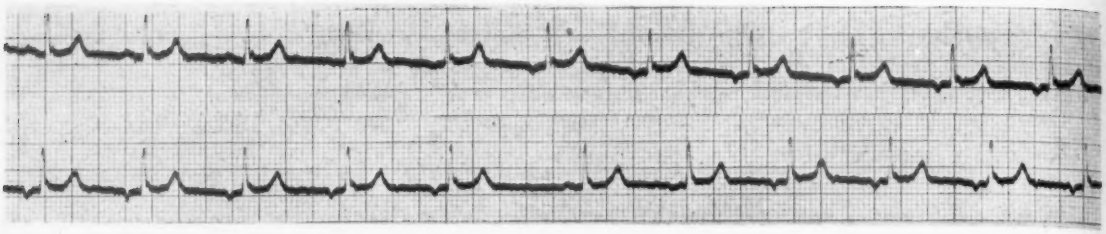

Fig. 4. The two tracings are continuous. The top tracing shows the gradual change from sinus rhythm into coronary sinus rhythm; in the bottom tracing coronary sinus rhythm suddenly ends with a longer pause and after two sinus beats coronary sinus rhythm reappears.

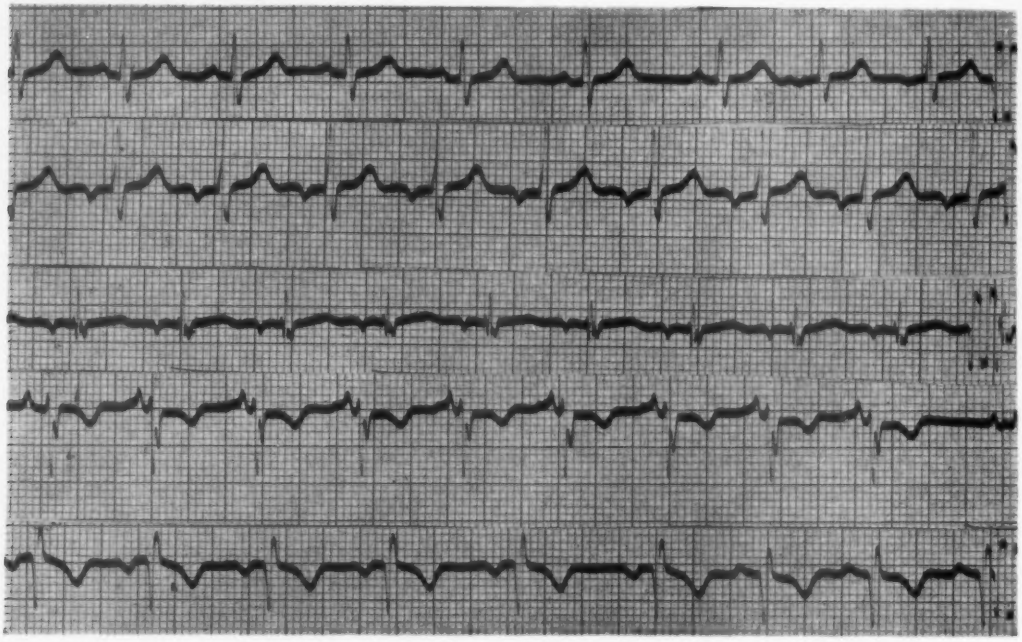

Fig. 5. The tracings were obtained from a 13-year-old child with rheumatic mitral valvular disease and congestive cardiac failure. The tracings are taken in the three standard leads, in V_1 and aVR. In lead 1, V_1 and aVR coronary sinus rhythm starts prematurely. It ends suddenly in V_1.

the ectopic rhythm is gradual. In Figure 4 (upper) a coronary sinus rhythm appears, gradually replacing the sinus beats and combination forms of the P waves can be seen. However the end of the abnormal rhythm is sudden as in Figure 4 (lower) where again there is a gradual transition from sinus to coronary sinus rhythm.

In Figure 5 the sudden onset and termination of the abnormal rhythm are demonstrated. This feature is not constant; the abnormal rhythm begins suddenly in lead I and aVR but not in V_1 where it appears gradually. However in this lead it ends suddenly.

Finally, in Figure 6 the ectopic rhythm ends suddenly three times. Close examination of the tracing shows that before the coronary sinus rhythm begins there is an acceleration of the sinus rhythm; conversely there is a slowing of the sinus rhythm when the coronary sinus rhythm ends. It is probable that the beginning and end only appear sudden because of the sudden inhibition of the heart with slowing of the rate. The A-V node may be more inhibited by the vagus nerve so that sinus rhythm can reappear.

Thus, the premature appearance of a new rhythm need not mean that this rhythm is heterogenetic and that we are dealing with extrasystoles or a paroxysmal tachycardia. Only if the coupling is found to remain constant

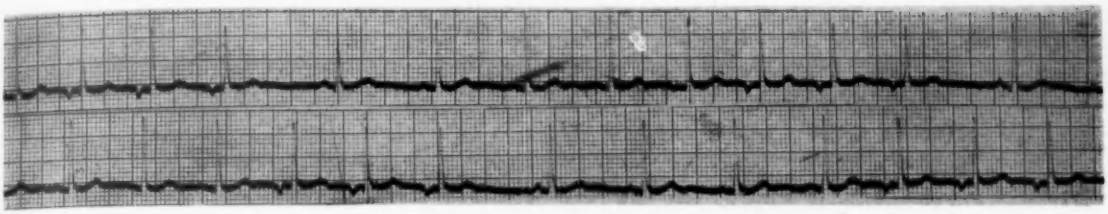

Fig. 6. Coronary sinus rhythm changes three times into sinus rhythm with a longer pause after the last coronary sinus beat. The beginning of the coronary sinus beats is also premature.

in several tracings can an ectopic extrasystolic rhythm be assumed to exist.

During the presence of coronary sinus rhythm the impulses reversely conducted to the atria may reach the sinus node, excite it and thus disturb the impulse formation in this structure. When the coronary sinus rhythm has stopped this process is known to depress sinus node activity to various degrees depending on the individual. Therefore, a pause simulating a post-extrasystolic pause is created. In fact, even one impulse reaching the sinus node from another center produces such an effect.[7]

These observations lead us to conclude that neither the rate nor the sudden appearance and/or termination of a coronary sinus rhythm can permit one to differentiate between the different forms of this rhythm.

Summary

(1) Certain characteristics of coronary sinus rhythm are discussed.

(2) Three main forms of this arrhythmia are recognized.

(3) It is shown on clinical observation that the differentiation of these three forms and therefore the evaluation of each case may meet with great difficulties in practice.

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Paroxysmal Atrial Tachycardia with Atrioventricular Block*

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ATRIAL TACHYCARDIA with block was first recognized almost 50 years ago by Sir Thomas Lewis whose description, using polygraphic observations, was published in 1909.[1] The initial electrocardiographic studies of the arrhythmia were then reported by Koplik in 1917,[2] and during the succeeding years various authors have described their experiences with this abnormal rhythm in patients with and without demonstrable heart disease.[3–6]

More recently, Enselberg *et al.*[7] and Lown *et al.*[8] have confirmed the earlier observation of Luten[9] that this arrhythmia may be precipitated by the excessive administration of digitalis and have stressed the relative frequency of this occurrence. Nevertheless, atrial tachycardia with block is generally considered to be an uncommon event, its recognition frequently overlooked and its significance often misunderstood. Confusion with atrial flutter or atrial fibrillation is particularly apt to occur although the management and clinical course of these two arrhythmias may differ significantly from that of atrial tachycardia with block, particularly in the presence of digitalis intoxication.

The arrhythmia is characterized by the following distinctive features:[8]

(1) Atrial rate usually varying between 150 to 250 per minute.

(2) Varying degrees of atrioventricular block, frequently 2:1 or of Wenckebach type.

(3) An isoelectric baseline between P waves.

(4) Increase in the degree of atrioventricular block with vagal stimulation.

(5) Occasional persistence of the arrhythmia for weeks or even months.

During the period between 1953 to 1956, 40 episodes of atrial tachycardia with atrioventricular block occurring in 39 patients have been observed at the Jewish Hospital of St. Louis. It is the purpose of this presentation to review our experiences with these cases.

METHOD OF STUDY

All electrocardiograms (16,481 records on 8,147 patients) taken in this hospital during the years 1953 to 1956 were studied. Each electrocardiogram was reviewed individually in order to eliminate any possible errors in the original interpretation of the record. Only those

TABLE I

Clinical Data Concerning 40 Episodes of Atrial Tachycardia with Block

	Digitalis intoxication	Digitalis intoxication not present
Sex	9 male 7 female	12 male 12 female
Age	30–80 yr	30–86 yr
Atrial rate	140–250/min	135–250/min
Atrioventricular conduction disturbance	Usually 2:1 A-V block or Wenckebach conduction. Simultaneous atrial and nodal tachycardia present on three occasions	Usually 2:1 A-V block or Wenckebach conduction
Type of heart disease	10 arteriosclerotic 4 rheumatic 2 hypertensive	19 arteriosclerotic 4 rheumatic 1 hypertensive

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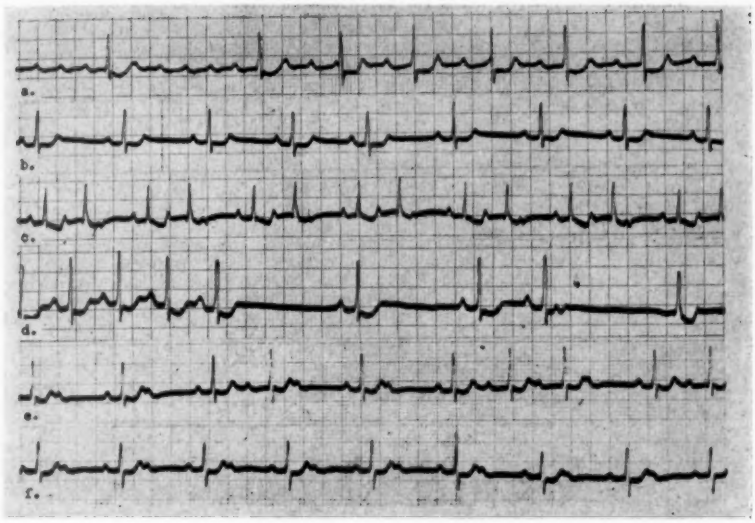

Fig. 1. R. G. (Case 4, Table II). (a) Record taken on 11/1/52. Atrial rate 220; ventricular rate 65 with varying 3:1 to 6:1 atrioventricular block. (b) Sinus rhythm present on 11/9/52. (c) Record taken on 2/17/56. Atrial rate 170 with Wenckebach periods. Digitalis intoxication present. (d) Record at time of conversion to sinus rhythm with intravenous magnesium sulfate administration on 2/17/56. (e) Rapid, slightly irregular atrial rate with Wenckebach periods. (f) Rate similar to (e) with 2:1 atrioventricular block.

electrocardiograms conforming to the criteria previously listed were selected. The hospital records of the patients were then reviewed and in some instances the attending physician was consulted for further information. In order to compare the relative incidence, all cases of supraventricular (both atrial and nodal) tachycardia with normal atrioventricular conduction, which occurred during the four-year period, were also reviewed. During this period of time, in which 40 episodes of atrial tachycardia with block occurred in 39 patients, 50 cases of supraventricular tachycardia with normal atrioventricular conduction were encountered.

Results

The clinical data concerning the 40 episodes which comprise this series are outlined in Table I.

Incidence, Age and Sex: During the four-year period studied, an average of ten episodes of atrial tachycardia with block occurred yearly at this institution in which slightly more than 4,000 electrocardiograms were taken annually. Atrial tachycardia with block was four-fifths as frequent as supraventricular tachycardia with normal atrioventricular conduction. The two youngest patients were both 30 years of age while the oldest was 86. Twenty-three patients or almost 60 per cent were 65 years of age or more. The sex distribution was almost equal; 20 of the patients were male.

Relationship to Digitalis Intoxication: Sixteen episodes were considered to be associated with digitalis intoxication. In nine cases, digitalis had been administered but the patients were not considered to be intoxicated. In the remaining 15 instances, the patients had either not received digitalis for at least several weeks prior to the time that the arrhythmia was present, or had not taken any digitalis. One patient developed atrial tachycardia with block due to digitalis intoxication on one occasion but also experienced the rhythm with varying atrial rates unrelated to the administration of digitalis (Fig. 1).

Associated and Precipitating Factors: In all instances there was associated organic heart disease. Arteriosclerotic heart disease occurred most commonly by far, being present in 29 cases, while rheumatic heart disease (usually mitral stenosis and insufficiency) was present in eight cases and hypertensive cardiovascular disease

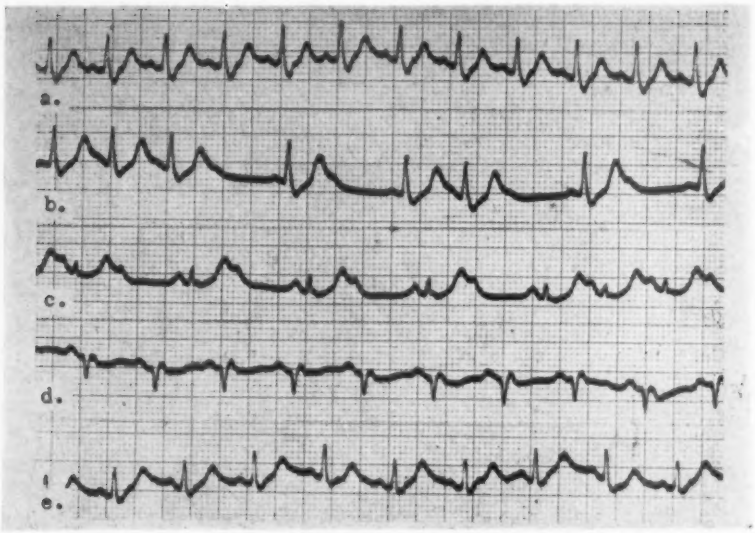

Fig. 2. Y. C. (Case 1, Table II). (a) Atrial tachycardia with atrial rate 150. (b) Record five hours later, showing intermittent 1:1 and 2:1 conduction (lead I). (c) Lead II taken at same time as b. (d) Sinus tachycardia present on following day, lead III. (e) Sinus tachycardia, lead V6.

in three cases. Eight patients developed the arrhythmia during the course of acute myocardial infarction. The administration of Isuprel® was the precipitating event for the occurrence of the arrhythmia in one patient in whom sinus rhythm and complete atrioventricular block was previously present.

Atrial and Ventricular Rates and the Degree of Heart Block: The atrial rates in our cases usually varied from 150 to 250 per min but were occasionally as slow as 135. No rates higher than 250 were encountered. There was no essential difference observed between the atrial rates of cases with and without digitalis intoxication (Table I). The ventricular rates were determined by the degree and type of atrioventricular block present, as demonstrated by the case shown in Figure 2. Occasionally, the block would appear only with the application of carotid sinus pressure. The degree of block generally varied from 1:1 conduction with increased P-R interval to Wenckebach periods and 2:1 or greater degrees of block. Wenckebach periods and 2:1 block were most frequently observed. Simultaneous atrial tachycardia and nodal tachycardia occurred in three patients, all of whom were intoxicated with digitalis. One of the cases is illustrated in Figure 3.

Treatment and Clinical Course: The clinical course of the patients varied considerably, somewhat depending on such factors as the type of therapy, etiology of the arrhythmia and the general clinical status of the patient. Recognized cases of digitalis toxicity when treated with potassium and the omission of digitalis

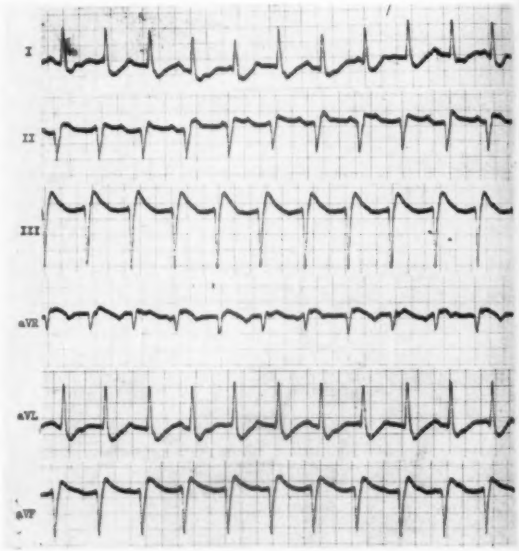

Fig. 3. B. F. Simultaneous atrial and nodal tachycardia associated with digitalis intoxication. (Reproduced from Shmagranoff, G. L. and Jick, S.: Simultaneous atrial and nodal tachycardia. *Am. Heart J.* (54: 417, 1957).

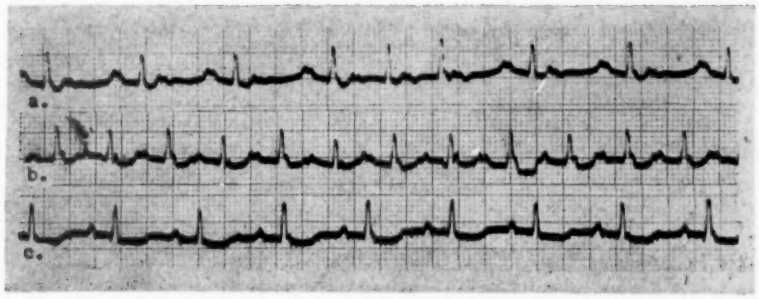

Fig. 4. C. J. (a) Initial record showing atrial rate 160 with 2:1 block and Wenckebach periods. Digitalis intoxication present. (b) Slowing of atrial rate during potassium chloride administration to 140, with prolonged atrioventricular conduction. (c) Sinus rhythm after conversion.

usually reverted promptly to sinus rhythm. Several cases with digitalis intoxication were not recognized immediately however and digitalis therapy was continued, often with increased dosage. These cases experienced a more protracted course. When given orally, a single dose of 3 grams of potassium chloride was usually sufficient. When the intravenous route was used, 40 meq of potassium chloride diluted with 500 cc of 5 per cent glucose in water was given. The rate of infusion varied from 60 to 80 drops per minute depending on the patient's ability to tolerate the pain along the course of the vein which frequently accompanies this procedure. Usually one such infusion was sufficient to restore sinus rhythm. In the presence of digitalis intoxication, treatment with potassium was associated with a slowing of the atrial rate and a disappearance of the atrioventricular block before sinus rhythm appeared (Fig. 4). Quinidine in large doses was sometimes efficacious and on one occasion, 10 cc of 20 per cent magnesium sulfate given intravenously terminated the arrhythmia when all other measures failed. Occasionally, atrial tachycardia with block was present for only a few moments and spontaneously disappeared, requiring no treatment at all. Withdrawal of digitalis alone was on several occasions associated with reversion to sinus rhythm.

Eleven patients in our series died during the hospitalization in which the atrial tachycardia with block occurred (Table II). Six of these 11 deaths were associated with acute myocardial infarction. In only one instance (No. 4, Table II) was the arrhythmia considered to be a contributing factor to the death of the patient who expired during a time when the atrial tachycardia was refractory to therapy and he was unable to tolerate the accompanying rapid ventricular rate.

Discussion

Although earlier reports have stressed the occurrence of atrial tachycardia with block in association with organic heart disease[4] without implicating digitalis intoxication, Lown and Levine[10] have recently emphasized the frequency with which episodes of this arrhythmia may be a manifestation of the toxic effects of digitalis. They have reported 66 episodes of atrial tachycardia with block occurring in 51 patients in whom 54 instances were directly related to digitalis toxicity. Twelve episodes were not related to the administration of digitalis. In addition, these authors have described a similar arrhythmia seen in the transition between atrial flutter and sinus rhythm during therapy with quinidine. Of their 12 patients in whom the arrhythmia was not related to digitalis intoxication, nine were said to have heart disease but the arrhythmia was stated to be "benign" and "idiopathic" in these instances. Other examples of idiopathic atrial tachycardia with block have been reported[11–14] but we have not observed any such cases. All instances of this arrhythmia in our series which were not precipitated by digitalis intoxication were associated with advanced degrees of organic heart disease.

Etiology

Varying etiologic factors may be associated with atrial tachycardia with block. In eight

TABLE II
Summary of the 11 Deaths

Patient	Age	Digitalis intoxication	Electrocardiographic findings	Comments
1. Y. C.	74	No	Atrial rate 140 with intermittent 2:1 block	Arteriosclerotic heart disease. Recent pulmonary embolus with numerous small pulmonary infarcts; purulent pericarditis
2. C. D.	36	Yes	Atrial rate 230 with 2:1 block	Rheumatic heart disease with subacute bacterial endocarditis. Vegetations on mitral valve with healed perforations
3. E. F.	55	No	Atrial rate 165 with 2:1 block; acute postero-lateral myocardial infarction	Acute myocardial infarction. Permission for autopsy not obtained
4. R. G.	47	Yes No	Atrial rates ranging from 150 to 220/min with varied A-V block	Rheumatic heart disease, with partial stenosis of mitral valve (mitral valvulotomy performed two years previously)
5. S. G.	73	Yes	Atrial rate 240 with changing A-V block	Arteriosclerotic heart disease. Permission for autopsy not obtained
6. K. K.	45	No	Atrial rate 150 with 3:1 and 2:1 block; acute posterior myocardial infarction	Acute myocardial infarction. Permission for autopsy not obtained
7. L. P.	55	No	Atrial rate 150 with Wenckebach periods; acute anteroseptal myocardial infarct	Acute anteroseptal myocardial infarction with rupture of ventricle at site of infarct
8. I. S.	76	Yes	Atrial rate 190 with Wenckebach periods	Acute myocardial infarction
9. K. S.	72	Yes	Simultaneous atrial and nodal tachycardia with A-V dissociation. Atrial rate 150. Ventricular rate 160	Acute myocardial infarction
10. B. Y.	76	Yes	Atrial rate 150 with 1:1 and 2:1 block	Acute anterior myocardial infarction
11. M. P.	78	No	Transient atrial tachycardia 170/min with 2:1 block; also sinus rhythm with complete heart block	Arrhythmia precipitated by isuprel therapy for heart block. Sinus rhythm spontaneously returned and patient expired several weeks later. Permission for autopsy not obtained

cases in our series, acute myocardial infarction was present. One of the patients developed the rhythm shortly after isuprel was administered sublingually for the treatment of complete heart block. Atropine has been similarly incriminated.[15] A case has been reported of this arrhythmia in association with bilateral cervical ribs,[6] with disappearance of the arrhythmia following surgical removal of the ribs. Purulent pericarditis has been reported in association with this arrhythmia[4] and this also occurred in one of our cases. Kuhn *et al.* have reported an episode of this rhythm occurring during cardiac catheterization.[16]

DIAGNOSIS

It is apparent that when this arrhythmia occurs, differentiation between digitalis intoxication and other etiologic factors may be a difficult and urgent problem. The efficacy of potassium administration where the arrhythmia has been precipitated by digitalis is well established.[7,8,10,17] However, potassium is of no therapeutic value in the absence of digitalis

intoxication. Accordingly, potassium administration has diagnostic significance as well as having excellent therapeutic value. The presence of Wenckebach conduction or the production of increased block by carotid sinus pressure is of no diagnostic value since they may occur both with and without digitalis intoxication. Simultaneous atrial and nodal tachycardia was present in three of our cases, all of whom had known digitalis intoxication. One of these cases reported elsewhere,[18] was treated with intravenous potassium chloride which produced slowing of the atrial rate similar to that seen in the usual case of atrial tachycardia with block. It is considered probable that simultaneous atrial and nodal tachycardia is a form of atrial tachycardia with block, and all of the reported cases of the former arrhythmia have been associated with digitalis intoxication.[19–21]

In many respects, atrial tachycardia with block resembles other atrial arrhythmias. Lown has aptly termed this arrhythmia a "hybrid" resembling both atrial tachycardia and atrial flutter.[22] Indeed some similarities to sinus tachycardia may be noted. The frequency of 2:1 block and the increasing degree of block with vagal stimulation resemble atrial flutter. The atrial rate and isoelectric baseline however are similar to the characteristics of atrial tachycardia without block. Occasionally the atrial rate is slightly irregular and since the P waves usually look somewhat like the normal ones, a similarity to sinus tachycardia can be observed. Thus it is clear that we are confronted with a supraventricular rhythm which, while resembling other members of the family of supraventricular tachycardias, is a distinct and independent entity. Since the descriptive name "*atrial tachycardia with block*" has been most frequently used, considerable confusion has arisen between this arrhythmia and paroxysmal atrial tachycardia *per se*, although the resemblance is quite superficial and the differences far greater than the simple presence or absence of atrioventricular block. When digitalis intoxication is not implicated as an etiologic factor, the arrhythmia may be considered to be another type of ectopic supraventricular rhythm such as atrial flutter, atrial fibrillation, or paroxysmal atrial tachycardia and with somewhat similar significance. There appears to be a frequent association of this arrhythmia with acute myocardial infarction since this occurred in eight of our cases.

TREATMENT

Therapeutic measures depend on establishment of the etiology of the arrhythmia. When digitalis toxicity is suspected, prompt withdrawal of the drug and the use of potassium, either orally or intravenously, will usually terminate the arrhythmia. The choice of the intravenous or oral route depends largely on the clinical status of the patient. Occasionally the arrhythmia is associated with severe dyspnea and even shock, and in such instances treatment with intravenous potassium chloride infusions is indicated if at all feasible. Omission of digitalis alone will sometimes restore sinus rhythm in patients who do not have severe systemic symptoms associated with the arrhythmia. Pronestyl® is said to be useful in certain cases, as is quinidine, although large amounts of the latter are usually necessary. Magnesium sulfate has been previously reported to be useful in the therapy of atrial tachycardia with normal atrioventricular conduction,[23] and in one patient in our series it terminated an episode of atrial tachycardia with block when other measures failed. In Kuhn's case, digitalis successfully restored sinus rhythm.[16]

The prognosis in patients with atrial tachycardia with block depends largely on the recognition of the arrhythmia, proper therapeutic management, and on the underlying disease. Eleven patients in our series died during the hospitalization in which the arrhythmia occurred —a mortality rate of 28 per cent. In only one instance, however, was the arrhythmia thought to be a significant contributing factor to the death of the patient. Death in the other cases was a result of the underlying cardiac disease. Six of the deaths occurring among the eight patients in this series with acute myocardial infarction. Our experience indicates that a somewhat better prognosis can be expected with this arrhythmia than that expressed in the earlier report of Decherd *et al.*[3] in which a 55 per cent mortality was experienced during the hospitalization in which the arrhythmia occurred.

The general improvement in therapeutic measures now available, and the more frequent recognition of digitalis intoxication are probably responsible for the higher survival rate in our series. Nevertheless the mortality remains ominously high, and indicates that when this arrhythmia occurs it is frequently associated with advanced and severe heart disease, and may indicate a poor prognosis.

Summary

(1) During a four year period in which over 16,000 electrocardiograms were reviewed, 40 episodes of atrial tachycardia with block occurring in 39 patients were encountered. Fifty instances of supraventricular tachycardia with normal A-V conduction occurred during the same period.

(2) Sixteen episodes were associated with digitalis intoxication, while 24 were unrelated to digitalis administration. All patients were suffering from advanced organic heart disease. In the absence of digitalis toxicity, the occurrence of atrial tachycardia with block may be considered to be somewhat comparable in significance to the occurrence of other atrial arrhythmias.

(3) The atrial rates varied from 135–250 and the atrioventricular block was usually 2:1 or Wenckebach in type. Simultaneous atrial and nodal tachycardia occurred in three patients, all of whom were intoxicated with digitalis.

(4) When digitalis intoxication was present, the administration of potassium salts usually terminated the arrhythmia. In one instance, intravenous magnesium sulfate was efficacious. In the absence of excessive digitalis administration, potassium was of no therapeutic value.

(5) Eleven patients in this series died. In only one instance was the arrhythmia considered to be an important contributing cause in the death of the patient. Of the eight patients in this series with acute myocardial infarction, six died while in the hospital. The prognosis with the arrhythmia usually depended on the severity of the underlying heart disease.

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The Electrocardiogram and Vectorcardiogram in Various Degrees of Left Bundle Branch Block*

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WE HAVE recently had the opportunity to make observations that serve to delineate more clearly some of the problems investing the electrocardiographic and vectorcardiographic diagnosis of left bundle branch block.

During a routine yearly examination a patient who for 23 years has been under treatment by one of us (M. G.) for diabetes mellitus was found for the first time to have left bundle branch block. The patient has had no symptoms and has no other signs of heart disease, nor is he hypertensive. Upon application of carotid sinus stimulation the left bundle branch block was replaced by normal conduction. As the rate again increased the left bundle branch block returned, not abruptly, but in a graduation of degrees (Fig. 1). Since this phenomenon proved to be reproducible in this patient it occurred to us to record simultaneously, conventional electrocardiograms and vectorcardiograms. The cube, Frank, and tetrahedron frames of reference were employed.

The records obtained are of interest in several respects. In this paper we shall concern ourselves with the light that they throw upon the electrocardiographic and vectorcardiographic diagnosis of left bundle branch block and the problem of the distinction of this condition from anteroseptal infarction and left ventricular hypertrophy.

ANALYSIS OF TRACINGS

The records show that with slight degree of left bundle branch delay (Fig. 2A,b and 2B,b) the changes are so small that the presence of delay in conduction in the left bundle branch cannot be suspected either in the conventional leads or in the vectorcardiograms, unless, of course, they occur in such a sequence as that presented here. Had the change from the complexes of Figure 2A,b to those of Figure 2A,a, or from the vector loop of Figure 2A,b to the loop of Figure 2A,a, been observed in serial tracings on the same individual it might easily have been ascribed to change in the cardiac position or, in the case of the precordial leads, to change in the placement of the electrodes. If we examine the change from complex E to complexes D and A in Figure 1 it becomes obvious that the RS-T segment and T wave changes that occur as a result of slight change in conduction in the left bundle branch can be mistaken for the serial changes commonly observed in coronary insufficiency and early myocardial infarction.

With a slightly greater degree of delay in conduction in the left bundle branch (Fig. 2A,c) the duration of QRS is still not increased in striking degree. The R waves are small in the right precordial leads but these findings are common to anteroseptal infarction, left ventricular hypertrophy, left bundle branch delay and are also encountered in many normal

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electrocardiograms. The limb leads certainly do not suggest abnormality. At the same time the horizontal loop of the cube vectorcardiogram shows a figure-of-eight form but *there is no portion of the loop that is inscribed slowly*. Such figure-of-eight loops commonly occur in anteroseptal infarction. Thus, in the distinction of anteroseptal infarction from left bundle branch delay the horizontal loop of the cube vectorcardiogram may be as inadequate as the conventional leads.

the series of Figure 2 the complexes are typical of left bundle branch block and the vector loops are equally characteristic. Obviously, there are degrees of block in the series of Figure 1 that are not represented in the series of Figure 2A. Some of these are seen in the series made with the Frank and Wilson tetrahedron methods (Fig. 2B, C, D and E).

Discussion

Various authors have reported that the vec-

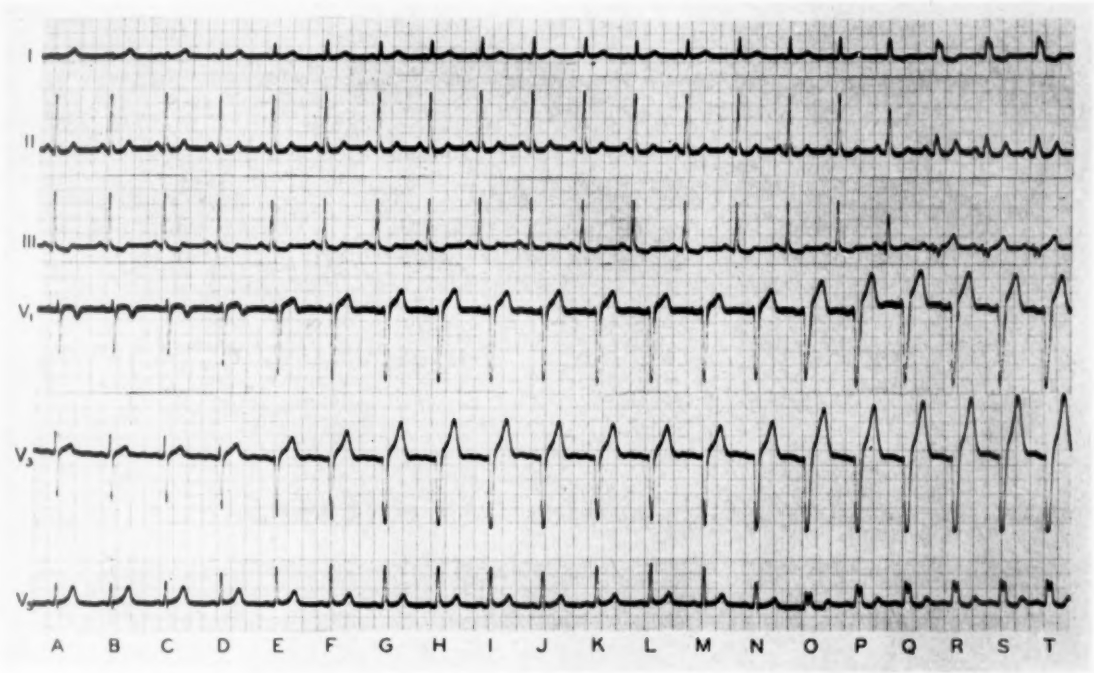

Fig. 1. Simultaneously recorded standard and simultaneously recorded precordial leads showing a progressive change in conduction from normal (beat *A*) to complete left bundle branch block (beats *P* through *T*). In tracings with precordial leads like those of beat *D* the presence of abnormal conduction might not be suspected, while complexes like those of beat *E* through *N* suggest anteroseptal infarction (marked diminution of R wave in anterior precordial leads) or left ventricular hypertrophy (deep, wide S waves in right precordial leads).

With the next greater degree of block shown in the series (Fig. 2A,d) the complexes show a form that is distinctly abnormal and that is common to anteroseptal infarction, left bundle branch block and left ventricular hypertrophy. The horizontal loop of the cube system shows a form that is common to left bundle branch delay and to anteroseptal infarction. Again there is no part of the vector loop that is inscribed slowly.

With the greatest degree of block shown in

torcardiogram is superior to the conventional electrocardiogram in one or another diagnostic area.[1,2] For the most part, their conclusions have been hasty and in some cases they rest upon unsound approach. Final proof of the presence of an anatomic lesion such as infarction resides, of course, in autopsy data. On the other hand, in the investigation of left bundle branch block autopsy material is useless. Satisfactory scientific proof of the existence of left bundle branch block against which any

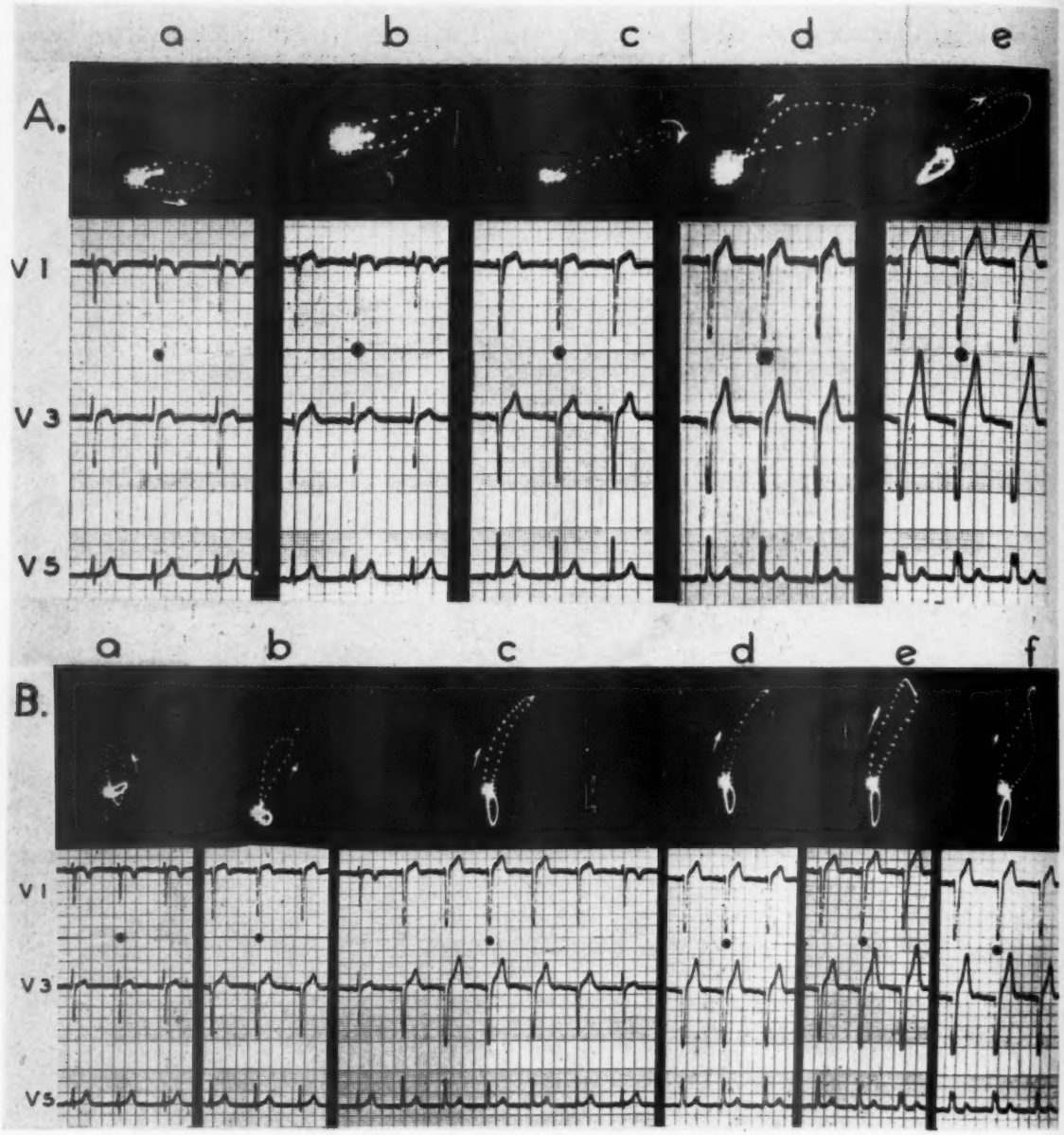

Fig. 2A and B. Vectorcardiograms in horizontal plane and simultaneously recorded precordial leads (marked by large dot between V_1 and V_2) illustrating normal conduction and varying degrees of left bundle branch block. (A). Vectorcardiogram recorded by cube system. (B). Frank system.

suggested electrocardiographic or vectorcardiographic criterion can be evaluated is difficult to obtain in humans. It is apparent that one can find unquestionable proof of the presence of left bundle branch block and more particularly the presence of left bundle branch block in the absence of other lesions, only when the opportunity is had to make observations on the same individual during the occurrence of repeated transitions from normal conduction to block of conduction in the left bundle branch. The presence of the normal complexes makes it possible to conclude that no other lesion (infarction, hypertrophy) is present; the rapid transition back and forth makes it possible to conclude that the change in the QRS form is

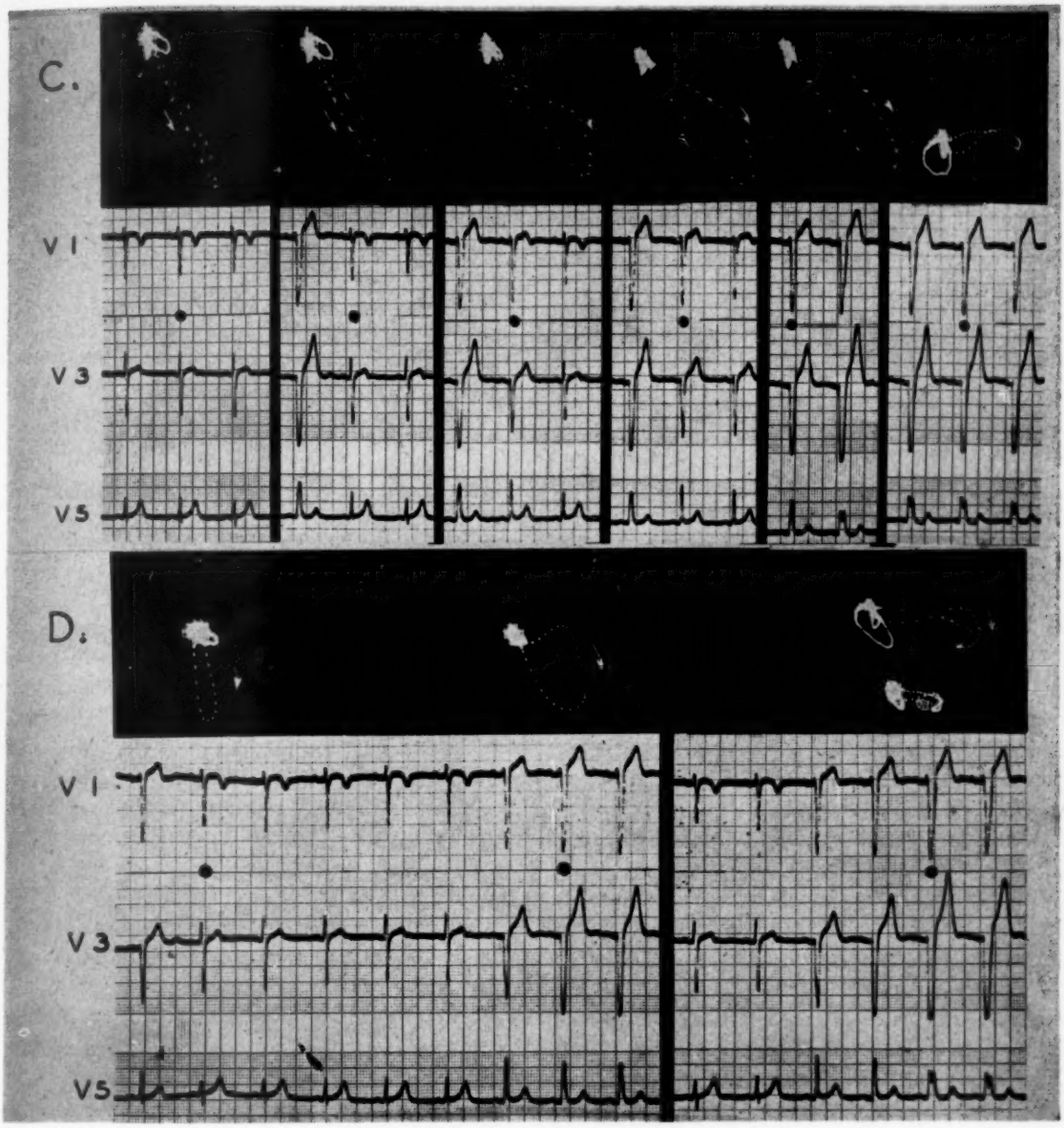

Fig. 2C and D. Vectorcardiograms in frontal plane and simultaneously recorded precordial leads. (C). Tetrahedron system. (D). Frank system. The third vector loop showing left bundle branch block is enlarged to $2^1/_2$ times the usual standardization.

due to conduction disturbance alone, for other lesions (with the possible exception of "injury") do not behave in this fashion. There is no evidence of injury phenomena in these records. Thus, one such series of observations as that presented here is of more value than a large number of observations in which the presence or absence of the conduction disturbance remains in some degree questionable and/or the absence of other lesions is "established" by inferences that may or may not be justified. Therefore, the following irrefutable conclusions are injected into the confusion that presently prevails:

Slight degrees of left bundle branch block may not be recognized either in the conventional electrocardiogram or the vectorcardiogram (cube or Frank system).

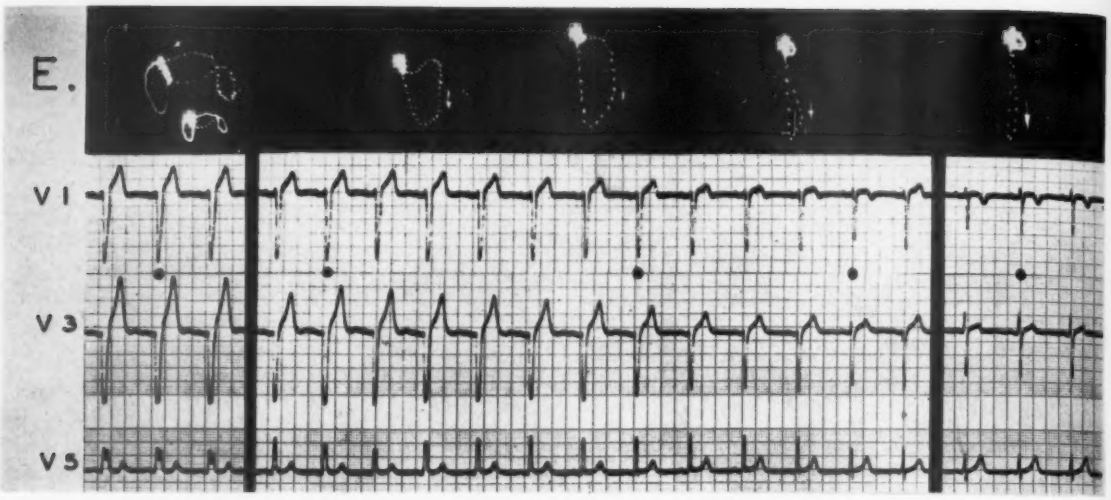

Fig. 2E. Vectorcardiogram in frontal plane (cube system) and simultaneously recorded precordial leads. The first vector loop showing left bundle branch block is enlarged to $2^1/_2$ times the usual standardization.

Slightly greater degrees of left bundle branch block may be present when the electrocardiogram shows low R waves in the right precordial leads that are commonly seen in normals, i.e., the record is within normal limits. At the same time the vectorcardiogram (cube, Frank) is distinctly abnormal, but shows a form that is common to both left bundle branch delay and some cases of anteroseptal infarction.

Until moderate degrees of left bundle branch block are reached no part of the vector loop is inscribed slowly. We believe that the same finding will be encountered in right bundle branch block.

A small R wave may be observed in the precordial leads that appears to have no counterpart in the vector loop of left bundle branch block. This is only one point that denies that the precordial leads can be derived by projection of the vector loops.

In connection with the problem of distinguishing left bundle branch block from anteroseptal infarction we should like to point out that it is possible when anteroseptal infarction and left ventricular hypertrophy are both present that slow inscription of the extremity of the vector loop may be observed. This matter will be taken up in some detail in a further paper dealing with the vectorcardiogram in left bundle branch block in terms of the path of accession.

Summary

Electrocardiograms and vectorcardiograms were recorded simultaneously from a patient with varying degrees of left bundle branch block. It was found that a slight degree of left bundle branch block is unrecognizable as an abnormality either in the electrocardiogram or in the vectorcardiogram (tetrahedron, cube, Frank). A slightly greater degree of left bundle branch block is not recognizable as an abnormality in the electrocardiogram but produces a definitely abnormal horizontal vectorcardiogram when the cube system is used. The latter, however, is not distinguishable from vectorcardiograms seen in some anteroseptal infarcts.

Varying slight degrees of left bundle branch block may produce a series of electrocardiograms that can be mistakenly interpreted as showing acute anteroseptal injury followed by ischemia.

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Post-Extrasystolic T Wave Changes*

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In 1944 Scherf[1] reported that in one-third of 168 patients with extrasystoles, changes occurred in the T waves of the first post-extrasystolic beat. Such changes were noted with auricular as well as ventricular extrasystoles, and occurred even during auricular fibrillation. Scherf[2] suggested that post-extrasystolic T wave changes might be indicative of heart disease. He attributed them to prolonged ventricular filling during the compensatory pause with resultant increase in diastolic heart size. The post-extrasystolic contraction then becomes a "stronger" one, and there may be a change in conductivity or in distribution of the electrical field during the recording of the T wave (which is registered during the height of the ventricular contraction).

Ashman *et al.*[3] studying the effect of cycle-length changes on the T wave, noted that in normal hearts T waves following a compensatory pause did not differ appreciably from the T waves of the regular complexes, but when the heart muscle was damaged marked changes might be seen. Levine, Lown, and Streeper[4] reported a study of 62 patients with post-extrasystolic T wave changes and felt that there was a high degree of correlation between such T wave changes and clinical evidence of heart disease. They reviewed the suggested explanations of these changes and concluded that the mechanism was not clear, although variations in cycle length and the mechanical effect of overdistention of the ventricles may be factors.

In 1954 Mann and Burchell[5] studied 46 patients with inversion of the T wave in the sinus beat following ventricular extrasystoles. They found that 43 of those patients had heart disease. In a control group of 46 patients with ventricular extrasystoles without subsequent T wave changes, heart disease was found in only twenty-six. Lepeschkin[6] relates the post-extrasystolic changes to the duration of the compensatory pause: when the pause is long, an upright T wave tends to become more upright in the post-extrasystolic beat while an inverted T wave tends to become more negative. He feels that major changes of the T wave are more common in heart disease. Videla[7] in an analysis of 60 examples was unable to confirm a relationship between the presence of T wave changes following extrasystoles and heart disease.

We studied this subject in an attempt to answer the following questions:

(1) Is the presence or degree of T wave change in the post-extrasystolic complex indicative of underlying heart disease?

(2) Does the degree of prematurity of the extrasystole or the duration of the compensatory pause have any determinant effect on the presence or absence of post-extrasystolic T wave changes?

(3) Does the administration of digitalis or quinidine predispose to post-extrasystolic T wave changes?

(4) Are the T wave changes associated with changes in other components of the post-extrasystolic beat, such as the P-R interval, QRS and QT duration, ST segment, and QRS contour?

Material and Methods

We studied in detail 84 examples of post-extrasystolic T wave changes occurring in 52 patients. The findings were compared with similar studies of 87 examples of premature contractions not exhibiting T wave changes after the compensatory pause, occurring in 42 patients selected at random. Pertinent clinical information concerning age, sex, and incidence

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of heart disease in both groups is presented in Table I. The etiology of the heart disease was

TABLE I

Age Incidence and Incidence of Heart Disease

Patients with post-extrasystolic T wave changes		52
Patients with heart disease		35 (67%)
Patients without heart disease		17 (33%)
	Age range	Average
19 Females	24–80 yr	57 yr
33 Males	9–82 yr	56 yr
Patients without T wave changes		42
Patients with heart disease		29 (69%)
Patients without heart disease		13 (31%)
	Age range	Average
16 Females	26–82 yr	57 yr
26 Males	35–71 yr	50 yr

similar in both groups, the vast majority being of hypertensive and/or arteriosclerotic origin.

The following data were noted for each example:

(1) The origin and frequency of extrasystoles (auricular, A-V nodal, ventricular).

(2) Lead of registration.

(3) R-R interval of the sinus beats preceding the extrasystole.

(4) R-R′ interval, i.e., the time between onset of the sinus beat and onset of a following extrasystole (R′).

(5) R′-R″ interval, i.e., the time between onset of the extrasystole and onset of the following sinus beat (R″).

(6) QT intervals in the sinus beat preceding the extrasystole, in the extrasystole (Q′T′), and in the sinus beat following the extrasystole (Q″T″).

(7) P-R intervals in the beats preceding and following the extrasystole.

(8) Presence or absence of changes in the ST segment, QRS complex and P wave, as well as in the T wave of the post-extrasystolic complex.

(9) Since the interval R′-R″ is a measure of the compensatory pause, and the ratio of the intervals R-R′/R-R expresses the degree of prematurity of the extrasystole, we set up a proportion between the compensatory pause and the degree of prematurity thus,

$$\frac{\text{R′-R″ (compensatory pause)}}{\text{R-R′/R-R (degree of prematurity)}}$$

or (R′-R″)(R-R)/R-R′, to determine if there were any consistent differences in this proportion in those examples which exhibited post-extrasystolic T wave changes and in those which did not.

(10) The presence of other electrocardiographic abnormalities.

(11) Clinical data with reference to age, sex, cardiac and other diagnoses, x-ray findings, and administration of digitalis or quinidine.

Of the 84 examples of post-extrasystolic T wave changes, 71 followed ventricular extrasystoles and 13 followed auricular extrasystoles. The control group consisted of 69 ventricular, 16 auricular and 2 nodal extrasystoles. The T wave changes, varied from minor alterations in amplitude to reversal of direction from positive to negative or *vice versa*. The types of T wave changes occurring in the post-extrasystolic complexes are summarized in Table II.

Results

Of the entire group of 94 patients, 64 (68%) had heart disease. Thirty-five (55%) of these 64 patients exhibited post-extrasystolic T wave changes. Of the 30 patients without demonstrable heart disease, 17 (57%) revealed similar changes. Reference to Table I will indicate that the percentage of patients with heart disease is essentially the same in the test sample and the control group. Neither the type of T wave change (Table II) nor the degree of change was of value in differentiating cardiac patients from those without heart disease. Thus, our data indicate that the occurrence of T wave changes in the beat following an extrasystole does not assist in determining the presence of clinically demonstrable heart damage. At least it does not do so in a hospital or office patient group where the percentage of cardiac patients is high. However,

TABLE II

Direction of Post-Extrasystolic T Wave Changes

(84 examples in 52 patients)

Direction of T in preceding sinus complex	T in post-extrasystolic complex					
	Upright	Inverted	Lower	Taller	Isoelectric	Diphasic
Upright		9	22	14	7	4
Inverted	2		5	1	1	
Isoelectric	5	6				
Diphasic	4	4				

these T wave changes might be more informative in mass screening programs where electrocardiography is one of the screening procedures.

The lead of registration, the site of origin, and the frequency of the extrasystoles were not found to be significant factors in determining post-extrasystolic T wave changes. We could not evaluate properly the relationship between the administration of digitalis and/or quinidine and the occurrence of post-extrasystolic changes since too few of our cases were receiving these drugs. Of the 52 patients with T wave changes, eight were receiving digitalis and three quinidine; of the 42 patients without changes, two were receiving digitalis, two quinidine, and one both.

The degree of prematurity of the extrasystole, the duration of the compensatory pause, and the ratio between these measurements as formulated above did not exhibit any consistent differences in the examples with or without post-extrasystolic T wave changes. In addition, neither the ratio of the degree of prematurity to the underlying sinus rate (i.e., R-R′/R-R) nor the ratio of the compensatory pause to the sinus rate (i.e., R′-R″/R-R) were found to be significantly different in the two groups.

Changes in other components of the post-extrasystolic complex were noted. The ST segment was depressed in five examples, elevated in three; the P-R interval was shortened in three instances; the QRS complex exhibited minor changes in six cases and a major change in one in that a basic left bundle branch block pattern reverted to normal conduction for the post-extrasystolic beat. The Q-T interval showed no changes in about one-third of the examples, was prolonged in another third, and shortened in the remainder. These changes in other components of the post-extrasystolic complex were not consistently associated with T wave changes and occurred with approximately equal frequency in patients with and without heart disease.

Summary

(1) We compared 84 examples of premature contractions followed by post-extrasystolic T wave changes with 87 examples of premature contractions not followed by such changes.

(2) Our data does not indicate any relationship between the presence or degree of post-extrasystolic T wave change and the existence of clinical heart disease.

(3) The degree of prematurity of the extrasystole and the duration of the compensatory pause did not have any demonstrable determinant effect on the presence or absence of post-extrasystolic T wave changes.

(4) Changes in other components of the post-extrasystolic complex occurred frequently but were not necessarily associated with T wave changes and did not differ appreciably in incidence in the cardiac and noncardiac groups.

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Experimental Studies

Excretion Products of Meralluride (Mercuhydrin)*

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CERTAIN organomercurial compounds are effective diuretics and are used extensively in congestive heart failure patients. Organomercurials probably act by reversible inhibition of enzyme systems necessary for reabsorption of water and electrolytes. The exact structure of the active enzyme inhibitor is not known but has been inferred by some to be a degradation product of the organomercurial and by others to be inorganic mercury. No data are available to substantiate either assumption.

This report will present data on patients to whom meralluride (Mercuhydrin®) has been given. Chromatographic analysis of the urine from these patients is used to obtain information on the excretory products of the organomercurial compound.

METHODS

In the current investigation meralluride (mercuhydrin) was found to be selectively adsorbed by passing it through a chromatography column of acid aluminum oxide. Inorganic mercury and noncarboxylic mercury compounds were not adsorbed. Therefore, using meralluride as the organomercurial diuretic, preliminary observations on the form and rate of mercury excreted in the urine were made in normal subjects and patients with heart failure.[1] These observations have now been extended and also include observations on the organomercurial (meroxyl) which has not been combined with theophylline and on the response in mercurial resistant patients.

Two groups of individuals who received meralluride were studied. The first group was composed of normal control subjects. The meralluride was administered intravenously to six, intramuscularly to six, and subcutaneously to four subjects. Two of these subjects also received meroxyl (meralluride [mercuhydrin] is meroxyl combined with theophylline) for comparative purposes in order to estimate the effect of theophylline, if any, on the excretory rate and excretory products of the organomercurial compound.

Two normal subjects were studied (Table II) in whom the urine was collected in three-hour fractions for a total of nine hours following the administration of meralluride by the three different routes of administration. These studies were done using shorter collection periods in order to determine more precisely when the maximum urinary excretion of meralluride occurred.

The second group of individuals who received meralluride consisted of 12 patients with cardiac failure. The etiology of the heart failure in all of the patients was arteriosclerotic heart disease. Nine of these were responsive to diuretics (Table III) in that significant increases in sodium and water excretion were observed

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TABLE I

Observations on Water, Electrolyte, and Mercury Excretion in Normal Subjects Given Meralluride by Three Different Routes

Patient	Urine volume ml C	1A	2A	3A	4A	Total	Fraction E mg Hg 1A	2A	3A	4A	Total	% rec.	Fraction B mg Hg 1A	2A	3A	4A	Total	% rec.
Observations following intravenous administration (2 ml = 78 mg meralluride Hg)																		
1. M.	620	1830	1490	820	430	4570	48.17	14.51	3.01	0.75	66.44	85.2	0.86	0.81	0.22	0.03	1.92	2.5
2. T.	890	1695	1585	980	900	5160	47.53	12.18	1.95	0.71	62.37	80.0	0.35	0.31	0.05	0.08	0.79	1.0
3. L.	240	1540	225	135	72	1972	59.98	6.76	3.46	0.15	70.35	90.2	0.99	0.14	0.17	0.09	1.39	1.8
4. Q.	760	1190	705	585	455	2935	58.10	6.00	1.64	0.21	65.95	84.6	0.63	0.83	0.09	0.01	1.56	2.0
5. S.	340	1090	310	—	475*	1875	54.68	6.24	—	1.26*	62.18	79.7	0.58	1.02	—	0.85*	2.45	3.1
6. M.	400	910	620	410	310	2250	49.20	15.60	2.01	0.60	67.41	86.4	0.90	0.72	0.45	0.10	2.17	2.8
Mean	542	1376	823	586	440	3127	52.94	10.22	2.41	0.61	65.78	84.4	0.72	0.64	0.20	0.19	1.71	2.2
% of control		254	152	108	81													
Per cent of meralluride mercury given							68	13	3	1	85		0.9	0.8	0.3	0.2	2.2	
Observations following intramuscular administration (2 ml = 78 mg meralluride Hg)																		
1. M.	595	1570	756	684	320	3330	45.95	8.30	2.38	0.72	57.35	73.5	0.25	0.16	0.11	0.10	0.62	0.8
2. T.	450	1975	740	430	830	3975	34.19	10.36	1.68	2.00	48.23	61.8	1.62	0.43	0.06	0.30	2.41	3.1
3. L.	250	800	315	140	72	1327	56.70	12.40	2.94	0.58	72.62	93.1	1.06	0.42	0.21	0.14	1.83	2.4
4. Q.	420	1335	855	650	255	3095	53.95	11.67	2.86	0.50	68.98	88.4	1.23	1.11	0.59	0.23	3.16	4.1
5. S.	600	1475	610	—	370*	2455	52.26	12.26	—	1.38*	65.90	84.5	1.03	0.29	—	1.18*	2.50	3.2
6. M.	700	1408	690	640	680	3418	52.59	9.72	1.77	0.61	64.69	82.9	0.43	0.44	0.10	0.00	0.97	1.2
Mean	503	1427	661	509	421	2933	49.27	10.79	2.33	0.97	62.96	80.7	0.94	0.48	0.21	0.33	1.92	2.5
% of control		284	131	101	84													
Per cent of meralluride mercury given							63	14	3	1	81		1.2	0.6	0.3	0.4	2.5	
Observations following subcutaneous administration (2 ml = 78 mg meralluride Hg)																		
1. M.	445	1220	1162	700	271	3353	44.08	13.43	2.63	1.22	61.36	78.7	0.54	0.44	0.25	0.10	1.33	1.7
2. Q.	520	885	925	495	345	2650	46.30	15.30	2.59	1.23	65.42	83.9	0.38	0.44	0.22	0.25	1.29	1.7
3. S.	200	955	410	185	100	1650	53.78	10.20	1.22	0.40	65.60	84.1	0.54	1.17	0.67	0.23	2.61	3.3
4. M.	440	940	550	760	355	2605	54.74	7.55	1.99	0.27	64.55	82.8	0.60	0.27	0.25	0.03	1.15	1.5
Mean	401	1000	762	535	268	2565	49.73	11.62	2.11	0.78	64.23	82.4	0.52	0.58	0.35	0.15	1.60	2.1
% of control		249	190	133	67													
Per cent of meralluride mercury given							64	15	3	1	82		0.7	0.7	0.4	0.2	2.1	

* Includes both periods 3A and 4A.
C = Control—average of two six-hour urine collection periods before diuretic given.
1A = First six-hour urine collection period after meralluride administration.
2A = Second six-hour urine collection period after meralluride administration.
3A = Third six-hour urine collection period after meralluride administration.
4A = Fourth six-hour urine collection period after meralluride administration.

following the administration of meralluride. Five patients received the meralluride intravenously and six received it intramuscularly. There were three patients who were resistant to all forms of therapy (Table IV), including meralluride, aimed at alleviation of congestive heart failure. One of these received meralluride both intravenously and intramuscularly. One resistant patient (No. 2, S.) received the drug by the intravenous route and one received it by the intramuscular route only.

Prior to administration of the meralluride, both to the noncardiac and cardiac patients, two six-hour-control specimens of urine were collected. The volume of urine during these control periods as well as the excretory rates of sodium, po-

TABLE I—Continued

Observations on Water Electrolyte, and Mercury Excretion in Normal Subjects Given Meralluride by Three Different Routes

Unchromatographed urine mg Hg						Urine sodium total meq						Urine potassium total meq			
1A	2A	3A	4A	Total	% rec.	C	1A	2A	3A	4A	C	1A	2A	3A	4A
Observations following intravenous administration (2 ml = 78 mg meralluride Hg)															
50.33	15.94	2.85	1.08	70.20	90.0	18	132	58	14	4	11	29	31	14	13
48.65	12.60	1.94	0.87	64.06	82.1	40	157	99	39	31	18	20	29	10	21
60.60	6.73	3.88	0.28	71.49	91.7	16	189	22	9	18	7	21	9	11	7
57.60	6.52	1.51	0.19	65.82	84.4	87	202	77	64	34	24	19	18	21	17
55.59	7.92	—	2.53*	66.04	84.7	44	179	60	—	55	26	35	11	—	31
50.12	16.64	3.01	1.10	70.87	90.9	56	146	94	36	40	12	24	29	16	18
53.82	11.06	2.64	1.01	68.08	87.3	44	168	68	32	30	16	25	21	14	18
							382	155	73	68		156	131	88	113
69	14	3	1	87											
Observations following intramuscular administration (2 ml = 78 mg meralluride Hg)															
45.21	8.51	1.92	0.24	55.88	71.6	—	—	—	—	—	—	—	—	—	—
38.32	10.88	1.97	2.67	53.84	69.0	37	227	71	26	58	9	16	15	6	23
60.40	13.70	3.89	0.99	78.98	101.3	6	83	26	7	16	10	22	20	8	6
55.40	12.00	3.28	0.59	71.27	91.4	27	140	96	66	21	12	27	24	23	12
53.25	12.33	—	3.01*	68.59	87.9	90	220	95	—	37	16	16	16	—	25
53.79	10.75	1.96	0.80	67.30	86.3	42	110	48	27	24	20	30	19	10	20
51.06	11.36	2.60	1.38	65.98	84.6	40	156	67	32	31	13	22	19	12	17
							390	168	80	78		169	146	92	131
65	15	3	2	85											
Observations following subcutaneous administration (2 ml = 78 mg meralluride Hg)															
44.52	13.36	3.67	1.31	62.86	80.6	58	114	43	37	15	32	24	9	10	13
45.14	15.54	3.27	1.36	65.31	83.7	77	159	144	39	28	24	20	28	13	14
58.06	12.14	2.34	0.69	73.23	93.9	22	138	70	21	7	9	17	8	5	6
56.21	7.81	2.19	0.36	66.57	85.3	28	114	43	37	15	18	24	9	10	13
50.98	12.21	2.87	0.93	66.99	85.9	46	131	75	34	16	21	21	14	10	12
							285	163	74	35		100	67	48	57
65	16	4	1	86											

Total = Total for 24-hour period.

% rec. = Per cent of meralluride mercury recovered in urine for entire 24-hour period, i.e. per cent recovered (% C) = $\frac{UC \times UV}{78} \times 100$.

Fraction E = Adsorbed fraction.
Fraction B = Nonadsorbed fraction.

tassium, and mercury (if any) were measured. The meralluride was then administered (2 ml = 78 mg meralluride Hg), and the urine was collected at six-hour intervals for the next 24 hours (with the exception of two normal subjects when three-hour-collection periods were used). Each specimen was passed through the chromatography column (Fig. 1) and the fractions were analyzed for mercury. Urinary sodium and potassium excretion rates were determined. The serum electrolytes (sodium, potassium and chloride) were found to be within normal limits in all of the patients studied.

Meroxyl was given to two normal subjects and to one patient who was in heart failure. The normal subjects received 2 ml (equivalent to 78

mg Hg) of meroxyl by the intramuscular and intravenous routes but not subcutaneously. The patient who was in heart failure received the drug by all three routes. Observations were made using this drug in order to observe the effect of the theophylline in the meralluride combination since meroxyl and meralluride are identical organomercurial compounds except for the addition of theophylline to the latter.

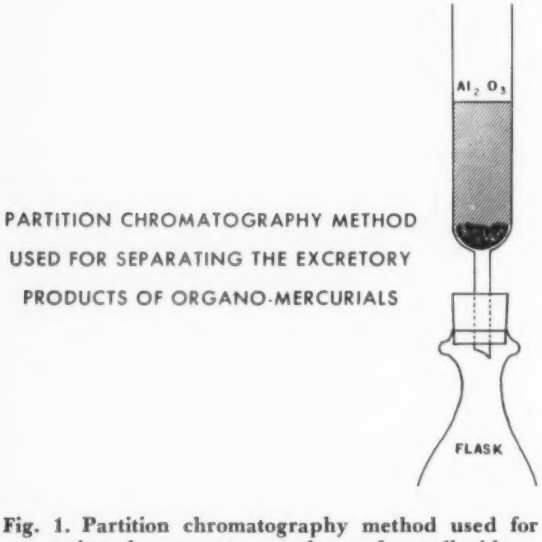

Fig. 1. Partition chromatography method used for separating the excretory products of meralluride.

Results

Noncardiac subjects rapidly excreted the drug predominantly in a form adsorbed by the column. Table I summarizes the observations on meralluride mercury recovered from the urine during successive six-hour-collection periods following administration of meralluride by the different routes. About 68 per cent was excreted in the adsorbable form (meralluride mercury) in the first six hours when given by the intravenous route and 63 per cent and 64 per cent after the intramuscular and subcutaneous routes respectively. By the end of 24 hours, 80 to 85 per cent had been excreted. Of the mercury recovered, less than 3 per cent was in the degraded (non-meralluride Hg) form following administration by any route. Although the amounts are too small to be significantly different, it appears that the major part of the degraded form was also excreted during the first six hours.

Table I also summarizes the sodium and potassium excretion rates in total milliequivalents during successive six-hour periods following administration of meralluride. The period of maximum sodium, water and mercury excretion coincided, and the curves for sodium and mercury elimination paralleled each other throughout the twenty-four hours. By the end of eighteen hours, the sodium excretion fell below the control values and remained there for at least the next six hours. Potassium excretion was not changed significantly throughout the twenty-four hour period. Mercury in the degraded meralluride fraction comprised an insignificant amount, being less than 1 mg in any one period which is insufficient to produce diuresis.

When three-hour urine collection periods following meralluride administration were used, the excretory rate during the first period was more dependent on the route of administration (Table II). Following intravenous administration to two subjects, about 60 per cent of the administered meralluride was excreted within the first three hours and less than 10 per cent during the second three-hour period. However, following the administration of meralluride by the intramuscular route, only an average of 38 per cent was excreted during the first three hours but 19 per cent was excreted during the subsequent three-hour period. Thus, when the amount excreted for both periods was combined the excretion rate was about the same by either route. When the intramuscular and subcutaneous routes of administration were compared in one patient, the excretion rate was only slightly less rapid following the subcutaneous route. As noted previously, the excretion rate of degradation products of meralluride in these subjects was less than 5 per cent of the administered mercury.

In the cardiac patients responding to meralluride, and in the noncardiac subjects, mercury was excreted in a qualitatively similar manner. Here again, (Table III) the maximum period of meralluride mercury excretion was during the first six hours following drug administration but the amount ranged from 29 mg (37 per cent) to 45 mg (58 per cent) after intravenous injection and from 13 (17 per cent) to 42 (54 per cent) after intramuscular injection. Excretion rate following intravenous administration was ap-

TABLE II

Excretion Rate of Meralluride Mercury Using Three Successive, Three-Hour Urine Collection Periods (2 ml Meralluride Administered = 78 mg Hg)

Patient	Urine volume ml C	1B	2B	3B	Total	Fraction E mg Hg 1B	2B	3B	Total	% rec.	Fraction B mg Hg 1B	2B	3B	Total	% rec.	Unchromatographed urine mg Hg 1B	2B	3B	Total	% rec.	Route of administration
1. M.	275	650	400	310	1360	44.85	6.64	4.96	56.45	72.4	0.91	0.34	0.53	1.78	2.3	45.05	7.16	5.78	57.99	74.3	I.V.
2. H.	350	1150	370	450	1970	48.01	3.78	4.73	56.52	72.5	1.15	0.24	0.25	1.64	2.1	50.25	3.75	5.15	59.15	75.8	I.V.
3. H.	225	390	545	225	1160	35.93	14.61	2.14	52.68	67.5	1.72	0.82	0.97	3.51	4.5	40.56	15.87	4.57	61.00	78.2	I.M.
4. M.	150	618	330	205	1153	26.64	14.22	4.98	45.84	58.8	0.62	0.56	0.31	1.49	1.9	28.12	16.01	5.90	50.03	64.1	I.M.
5. H.	500	790	850	460	2100	27.50	12.33	5.06	44.89	57.6	1.74	0.94	0.51	3.19	4.1	28.24	12.87	5.75	46.86	60.1	S.C.

1B = First three-hour urine collection period after meralluride given.
2B = Second three-hour urine collection period after meralluride given.
3B = Third three-hour urine collection period after meralluride given.
See Table I for key to abbreviations.

TABLE III

Observations on Water and Mercury Excretion in Patients With Heart Failure Given Meralluride

Patient	Urine volume ml C	1A	2A	3A	4A	Total	Fraction E mg Hg 1A	2A	3A	4A	Total	% rec.	Fraction B mg Hg 1A	2A	3A	4A	Total	% rec.	Unchromatographed urine mg Hg 1A	2A	3A	4A	Total	% rec.
Observations following intravenous administration (2 ml = 78 mg meralluride Hg)																								
1. R.	410	880	765	435	365	2445	38.69	18.36	8.14	4.16	69.35	88.9	0.86	0.88	0.28	0.44	2.46	3.2	38.40	20.27	8.31	4.00	70.98	91.0
2. M.	550	840	795	880	820	3335	38.78	13.69	6.57	3.16	62.20	79.7	1.32	0.58	0.22	0.15	2.27	2.9	42.42	15.01	4.00	1.30	62.73	80.4
3. G.	500	810	494	—	400*	1704	45.14	20.22	—	11.66*	77.02	98.7	0.72	0.09	—	0.22*	1.03	1.3	48.20	16.68	—	12.60*	77.48	99.3
4. H.	550	624	695	—	710*	2029	34.56	23.75	—	16.90*	75.21	96.4	0.29	0.15	—	0.21*	0.65	0.8	39.47	25.85	—	8.21*	73.53	94.3
5. P.	420	785	815	1765	400	3765	29.01	21.12	14.35	4.10	68.58	87.9	1.14	1.09	1.50	0.98	4.71	6.0	30.21	21.60	13.25	5.18	70.24	90.1
Mean	486	788	713	1027	539	2656	37.24	19.43	9.69	8.00	70.47	90.3	0.87	0.56	0.67	0.40	2.22	2.8	39.74	19.88	8.52	6.26	70.99	91.0
Per cent of meralluride mercury given							48	25	12	10	90		1.1	0.7	0.9	0.5	2.8		51	25	11	8	91	
Observations following intramuscular administration (2 ml = 78 mg meralluride Hg)																								
1. H.	190	585	420	305	425	1735	13.22	24.95	17.69	14.79	70.65	90.6	0.34	0.27	0.17	0.20	0.98	1.3	14.37	24.26	18.00	15.19	71.82	92.1
2. M.	175	524	325	250	560	1659	41.08	8.68	2.31	0.68	52.75	67.6	0.43	0.11	0.01	0.00	0.55	0.7	41.96	8.73	2.43	0.78	53.90	69.1
3. A.	400	820	490	445	34	1789	21.07	17.92	9.42	0.70	49.11	63.0	0.15	0.24	0.06	0.01	0.46	0.6	22.47	18.38	10.79	0.78	52.42	67.2
4. S.	216	336	334	258	60	988	42.07	9.51	4.62	0.99	57.19	73.3	0.39	0.10	0.10	0.05	0.64	0.8	42.67	10.05	5.29	0.89	58.90	75.5
5. M.	450	460	545	710	440	2155	32.36	12.75	3.53	1.10	49.74	63.8	0.39	0.18	0.05	0.04	0.66	0.8	32.96	13.03	3.73	1.50	51.22	65.7
6. S.	234	480	425	56	100	1061	40.47	12.90	0.54	1.12	55.03	70.6	0.12	0.22	0.03	0.05	0.42	0.5	40.96	13.18	0.72	1.45	56.31	72.2
Mean	278	534	423	337	270	1565	31.71	14.45	6.35	3.23	55.74	71.5	0.30	0.19	0.07	0.06	0.62	0.8	32.57	14.61	6.83	3.43	57.43	73.6
Per cent of meralluride mercury given							41	19	8	4	71		0.4	0.2	0.1	0.1	0.8		42	19	9	4	74	

See Table I for key to abbreviations.

* Includes both periods 3A and 4A.

proximately two times greater during the second six-hour period in the cardiac patients than in the noncardiac subjects. Subsequently, the excretion rates were similar. After twenty-four hours the total mercury excreted, which ranged from 80 to 90 per cent of the injected mercury, was about equal in the normal and responsive cardiac patients. As in the normals, an insignificant amount (less than 3 per cent) was excreted as degradation products. In 48 hours or less, the excretion of mercury was complete in all patients. There was little difference in the mercury excretion rates between the intramuscular and subcutaneous routes of administration, but both were significantly less than the excretion rate when the intravenous route was used in patients with edema due to heart failure.

When meralluride was given intravenously to the cardiac patients there was a rather marked rise in sodium excretion which remained high for 18 hours but the maximum was during the first six hours. After intramuscular injection, there was a marked rise in sodium output and again the maximum period was during the first six hours. There was no significant effect on potassium excretion. The mercury excretion paralleled sodium excretion just as it did in the normal subjects.

Observations made on three cardiac patients who failed to respond to cardiac therapy, including meralluride, are presented in Table IV. The excretion rate of meralluride mercury was less than that observed in normal subjects but in only one of the patients was it significantly lower than that observed in responsive cardiac patients. When given intravenously, maximum excretion of meralluride mercury was observed during the first six-hour period. Following intramuscular injections the elimination was considerably delayed in one patient, the maximum excretion being in the last two six-hour periods and in the second patient the excretion rate of mercury was about evenly distributed throughout the four collection periods. Degradation products accounted for a significant percentage of the total mercury in one of the nonresponsive cardiac patients (Fig. 2) being 12 per cent after intravenous administration and 21 per cent after intramuscular administration. Possibly, this may be accounted for by the slower rate of excretion.

TABLE IV

Observations Following Administration of Meralluride to Patients Who Did Not Obtain a Diuretic Response

Patient	Fraction E mg Hg						Fraction B mg Hg						Unchromatographed urine mg Hg						Route
	1A	2A	3A	4A	Total	% rec.	1A	2A	3A	4A	Total	% rec.	1A	2A	3A	4A	Total	% rec.	
1. D.	26.61	17.22	3.54	3.02	50.39	64.6	2.22	6.11	0.89	0.32	9.54	12.2	29.22	23.45	5.08	3.65	61.40	78.7	I.V.
2. S.	41.61	7.90	2.10	1.18	52.79	67.7	0.16	0.07	0.04	0.04	0.31	0.4	41.21	8.31	2.18	1.48	53.18	68.2	I.V.
1. D.	3.20	3.25	19.11	13.18	38.74	49.7	5.07	1.79	3.68	6.18	16.72	21.4	8.07	5.15	24.73	22.83	60.78	77.9	I.M.
3. M.	12.41	11.66	6.50	11.86	42.43	54.4	0.35	0.12	0.07	0.09	0.63	0.8	12.80	11.81	6.28	11.47	42.36	54.3	I.M.

I.V. = Meralluride (2 ml) given intravenously.
I.M. = Meralluride (2 ml) given intramuscularly.
See Table I for key to abbreviations.

Theophylline appeared to enhance the excretion rate of the organomercurial following any of the three routes of adminstration since the recovery rate of mercury was significantly higher following the administration of meralluride than it was following the administration of meroxyl (Table V). Twenty-four hours after intravenous administration to normal subjects, only slightly more than half of the mercury administered as meroxyl was excreted when the drug was given by either the intravenous or the intramuscular route. A similar rate of excretion was observed in the cardiac patient following intravenous and intramuscular administration but following subcutaneous administration in one patient, only 37 per cent was recovered as meroxyl mercury. As in the case of meralluride, the degradation products amounted to less than 4 per cent of the administered meroxyl.

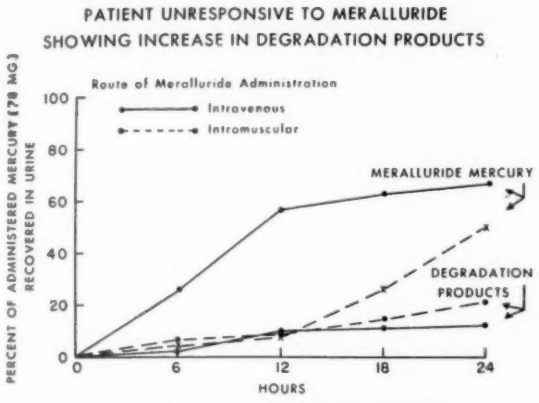

Fig. 2. Meralluride was administered to this patient with heart failure who was unresponsive to diuretic therapy. There was a marked delay in the excretion rate of meralluride mercury following intramuscular administration apparently due to the poor cardiovascular status and marked edema that this patient presented. Associated with the retention of the mercurial, the degradation products of meralluride increased significantly so that these amounted to 21 per cent of the total administered meralluride mercury or nearly one-third of the excreted mercury in the urine.

Discussion

It appears that meralluride is excreted primarily in the carboxylic form (adsorbed form). Mercury in the degraded meralluride fraction comprised an insignificant amount, being less than 1 mg which is insufficient to produce diuresis in any one period. About 50 to 60 per cent of the meralluride mercury is excreted within three hours in normal subjects following intravenous administration and 35 to 40 per cent is excreted following intramuscular administration. After six hours 60 to 70 per cent of the administered mercury is excreted following either route of administration. In the cardiac patients who responded to meralluride, mercury was excreted in a qualitatively similar manner to the normal subjects. There appeared to be a moderate delay in the cardiac patients following intramuscular administration. This was probably due to delayed adsorption in patients with an abnormal circulation and a slight increase in tissue fluid.

DeGraff, Batterman, and Lehman[3] found that when theophylline is combined with the organomercurials, it enhances both mercury excretion and diuresis initially but does not increase the total mercury excretion. The outstanding action of theophylline was reported to be increased absorption of the mercurial following intramuscular or subcutaneous administration. Our observations indicated that agreement since the excretory rate of mercury was greater following any route of administration when the organomercurial was combined with theophylline as meralluride by comparison to the response following the administration of meroxyl, which does not contain theophylline.

Meralluride, like all other organomercurials, seems to have its site of action in the proximal renal tubules where sodium and chloride are actively reabsorbed by an enzyme transport system.[4,5] In this same area, water is absorbed in a passive manner by back diffusion. Meralluride apparently inhibits the sodium or chloride reabsorbing mechanisms. Probably up to 35 per cent of the filtered sodium can be blocked from reabsorption by these compounds. This necessarily retains water in the renal tubule. When this fluid reaches the distal tubule, where water is actively reabsorbed, all the water and sodium cannot be reabsorbed and diuresis is manifested. Merrill demonstrated that in cardiac patients in congestive failure, renal blood flow is decreased one-third to one-fifth of the normal and glomerular filtration rate is decreased one-half to one-third of normal. It

TABLE V

Observations Following the Administration of Meroxyl

Patient	Urine volume ml						Fraction E mg Hg						Fraction B mg Hg					
	C	1A	2A	3A	4A	Total	1A	2A	3A	4A	Total	% rec.	1A	2A	3A	4A	Total	% rec.
1. T.	565	2360	1235	310	850	4755	32.32	10.44	0.03	0.18	42.97	55.1	2.65	0	0	0.05	2.70	3.5
2. Q.	470	930	185	124	253	1492	48.25	1.55	0.96	0.53	51.29	65.8	1.22	0.21	0.12	0.27	1.82	2.3
3. T.	502	1955	1320	1040	520	4835	22.14	9.67	6.74	1.94	40.49	51.9	0.60	0.38	0.25	0.24	1.47	1.9
4. Q.	415	930	770	640	725	3065	20.93	10.80	5.63	4.85	42.21	54.1	0.50	0.62	0.36	0.17	1.65	2.1
5. H.	750	1625	785	330	115	2855	50.05	7.99	1.89	0.45	60.38	77.4	1.13	0.28	0.22	0.13	1.76	2.3
6. S.	275	460	340	210	56	1066	30.50	3.02	4.56	1.97	40.05	51.3	1.93	0.01	0.21	0.15	2.30	2.9
7. S.	205	365	410	575	250	1600	8.72	4.52	12.18	3.15	28.57	36.6	0.21	0.12	0.37	0.23	0.93	1.2
8. S.	148	242	310	208	220	980	13.85	19.61	12.25	5.13	50.84	65.2	0.12	0.55	—	0.29	0.96	1.2

1A = First six-hour period after meroxyl administration.
2A = Second six-hour period after meroxyl administration.
3A = Third six-hour period after meroxyl administration.
4A = Fourth six-hour period after meroxyl administration.

seems probable that in the mercurial resistant patients that we studied, the cardiovascular–renal system was so badly damaged that they no longer responded to therapy because renal function was too severely depressed and glomerular filtration rate was inadequate to form urine. The condition of patients of this type becomes progressively worse in spite of therapy. Plasma electrolytes in these patients were within normal limits.

Summary and Conclusions

(1) It has been demonstrated by partition chromatography that practically all the mercury administered as meralluride (mercuhydrin) is excreted in a form closely resembling the administered drug.

(2) Degradation products of meralluride which are excreted in the urine amount to less than 5 per cent of the administered mercury in both normal subjects and patients with heart failure who obtain a diuretic response following administration of the drug.

(3) Sixty to 70 per cent of the meralluride is excreted within the first six hours and 80 to 85 per cent is excreted within 24 hours following drug administration to normal subjects and to patients in heart failure who obtain a diuretic effect from the drug.

(4) The sodium excretion rate and meralluride mercury excretion rate parallel each other.

(5) In normal subjects there is very little difference in excretion rates of meralluride following intravenous, intramuscular, or subcutaneous routes of administration. In patients with heart failure and edema there is a moderate delay in meralluride excretion following intramuscular administration during the first three hours but six hours after drug administration the amount of meralluride excreted is similar.

(6) In patients who did not obtain a significant diuretic response to meralluride there was a significant delay in mercury excretion. In one such patient the amount of mercury excreted as degradation products increased significantly being 12 per cent following intravenous administration and 21 per cent following intramuscular administration.

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TABLE V—Continued

Observations Following the Administration of Meroxyl

Fraction A mg Hg						Urine sodium total meq					Urine potassium total meq						
1A	2A	3A	4A	Total	% rec.	C	1A	2A	3A	4A	C	1A	2A	3A	4A	Diagnosis	Route of administration
34.93	10.34	0.05	0.09	45.41	58.2	39	242	93	12	55	9	11	18	3	12	Normal	I.V.
49.29	2.00	0.98	1.05	53.32	68.4	66	161	27	21	30	21	22	7	3	12	Normal	I.V.
22.87	9.54	6.97	2.21	41.59	53.3	17	162	75	46	22	11	18	17	16	18	Normal	I.M.
21.51	11.01	6.51	5.04	44.07	56.5	33	88	93	58	49	18	19	21	15	13	Normal	I.M.
50.70	8.16	2.10	0.67	61.63	79.0	66	260	90	24	9	18	25	12	11	10	Normal	S.C.
31.74	3.14	4.57	2.56	42.01	53.9	2	54	20	14	5	1	17	10	3	4	Cardiac	I.V.
9.02	4.54	12.52	3.10	29.81	37.4	3	14	8	17	17	5	15	6	17	14	Cardiac	S.C.
13.61	20.46	13.10	5.89	53.06	68.0	3	20	44	21	20	8	26	24	21	15	Cardiac	I.M.

I.V. = Intravenous administration of meroxyl (2 ml = 78 mg Hg).
I.M. = Intramuscular administration of meroxyl (2 ml = 78 mg Hg).
S.C. = Subcutaneous administration of meroxyl (2 ml = 78 mg Hg).

Review

Idiopathic Myocardial Hypertrophy*

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IDIOPATHIC myocardial hypertrophy is a curious disturbance of the heart which since its original description in 1901[1] has remained unexplained both to clinicians and pathologists. One important reason for the imperfect understanding of this disorder has been its comparative rarity and the resultant paucity of well studied examples. The following report summarizes our experience with eight cases and is submitted as an addition to the literature.

The subjects of this study were patients who died of heart disease and in whom the sole significant pathologic finding was myocardial hypertrophy. This enlargement involved primarily the left ventricle and was noted in the absence of coronary or valvular heart disease or renal arterial disease. At least eight patients fulfilling these criteria were admitted to the West Roxbury Veterans Administration Hospital between 1947 and 1956. Several others presented reasonably strong evidence for this diagnosis but were rejected from this report because of one or more equivocal clinical or pathologic findings.

Table I summarizes the salient features of these patients. The following two case narratives illustrate the problems encountered in this disease and are considered representative of this syndrome. Summaries of the remaining cases are appended at the end of the paper.

CASE HISTORIES

CASE 1. A 50-year-old white male carpenter was admitted because of belt-like lower anterior chest pain associated with slight dyspnea. He had been perfectly well until four months prior to admission. For two months he had become aware of increasing exertional dyspnea and one month before admission he was told that an x-ray had shown cardiac enlargement and pneumonia, for which he was digitalized. Despite this, he became gradually weaker but had no edema, orthopnea, hemoptysis or paroxysmal nocturnal dyspnea. The past history was not remarkable excepting for several attacks of "asthma" 26 to 28 years prior to admission which ceased completely when he stopped working as a florist.

The physical examination on admission revealed an apprehensive, though not overly distressed, middle-aged man. The blood pressure was 105/90, pulse 104, and temperature 98° F. The ocular fundi showed minimal arteriosclerotic changes. There were a few inspiratory rales and rhonchi together with decreased breath sounds at the right base. The heart was markedly enlarged. No murmurs were heard. The second pulmonic sound was loud, split, and exceeded A_2 in intensity. The liver edge was 3 to 4 cm below the costal margin. Venous pressure was 180 mm water; decholin circulation time 37 seconds; the vital capacity was 1.9 *l* in one second and totaled 3.1 liter.

Laboratory Data: Hemogram and urine were within normal limits. Cholesterol was 293 mg/100 ml; BMR plus 4 per cent; BUN 13 mg/100 ml; total protein 7.7 g/100 ml; albumin 4.9 g/100 ml; globulin 2.8. The VDRL test was negative. Sputum culture: normal flora. The ECG (Fig. 1) showed left ventricular hypertrophy and atrial enlargement. The chest film (Fig. 2) revealed cardiomegaly and pulmonary congestion. The IVP was normal.

Course: The patient was maintained on digoxin 0.25 mg twice daily, a low-sodium intake and mercurial diuretics. On the second day he developed pain, cyanosis and disappearance of pulses in the left foot. Regression of symptoms and signs coincided with heparin therapy. His dyspnea improved but he began to have transient confusional episodes. Two months after admission a chest film demonstrated infarction at the left base. On the 61st hospital day (eight days before his demise), he suddenly became very dyspneic, apprehensive and febrile (104°) and developed tachy-

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TABLE I

Cases of Idiopathic Myocardial Hypertrophy at West Roxbury Veterans Administration Hospital (1947–56)

	Age at onset of symptoms	Survival from onset of symptoms (months)	Blood pressure	Murmurs	Heart weight (g)	Principal antemortem diagnoses
1.	50	6	105/90	None	590	Idiopathic myocarditis
2.	31	60	138/86	Apical diastolic rumble Apical systolic Aortic systolic and diastolic	860	Rheumatic heart disease
3.	43	48	115/85	Apical systolic	650	Rheumatic heart disease
4.	52	42	120/90	Apical systolic	800	Myocardial disease of unknown etiology
5.	29	19½	150/90	Apical systolic	No exact record; "very markedly enlarged"	Myocarditis of unknown etiology
6.	32	3	108/86	Apical systolic	590	Myocarditis of unknown etiology
7.	40	84	130/84	Apical and basal systolic	No autopsy	Myocarditis of unknown etiology
8	26	1	106/80	None	550	Acute nonspecific myocarditis

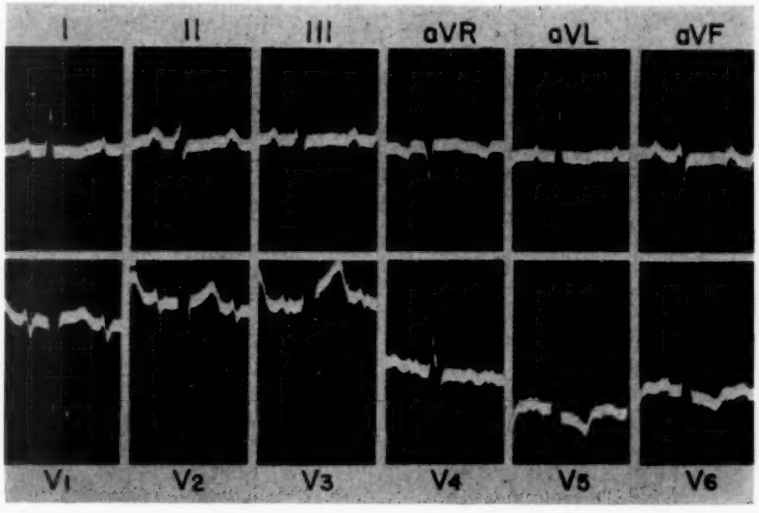

Fig. 1. Electrocardiogram in case I, showing left ventricular hypertrophy and atrial enlargement.

cardia. Roentgenogram of the chest suggested pneumonia or a new infarct in the left lower lobe. He was again given heparin, penicillin and streptomycin. Despite all treatment his downhill course persisted. Because of this steroid therapy was begun, but despite all efforts he continued to deteriorate.

Necropsy Data: No immediate cause of death was noted. There was an acute pulmonary infarction in the left lower lobe. The heart weighed 590 g and exhibited extensive left ventricular hypertrophy. The valves were normal and there were no significant coronary atheromata. There were organizing thrombi in both ventricles.

Microscopic examination showed myocardial hypertrophy with focal areas of necrosis. The renal arterioles were not remarkable.

Comment: This case illustrates the rapid course which may occur in idiopathic myocardial hypertrophy in a previously "well" individual. During his hospitalization, diagnoses of pericarditis, coronary disease and myocarditis were entertained, but discarded in favor of idiopathic myocardial hypertrophy. Chest pain and unremitting progressive congestive heart failure were the main clinical features in this patient.

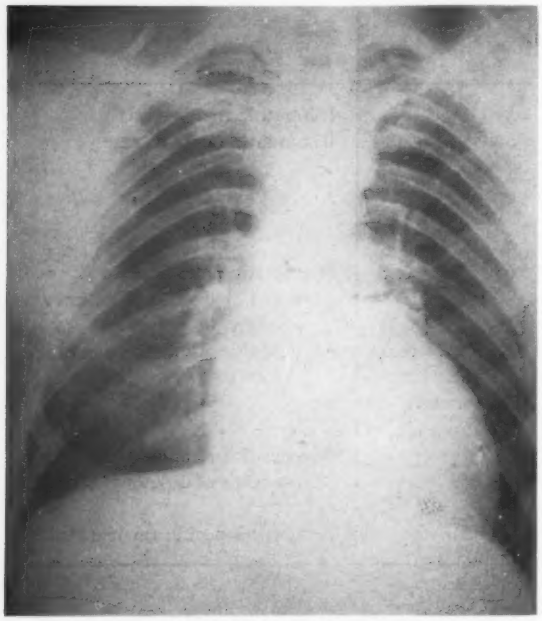

Fig. 2. Chest film in case I showing cardiomegaly due to left ventricular enlargement.

Case 2. This patient was first seen in March, 1952 when he was 33 years old. Two years earlier during a bout of pneumonia he was apprised for the first time of the presence of heart disease. In December, 1951 he was admitted to another hospital for exertional dyspnea and recurrent left chest pain. There the diagnosis of rheumatic heart disease was made and treatment with digitalis and salt restriction started. He entered West Roxbury Veterans Administration Hospital because of failure of symptomatic improvement. The previous history was unremarkable excepting for duodenal ulcer. The family history was noncontributory.

The patient was dyspneic, hoarse, and appeared chronically ill. The pulse was 112, blood pressure 138/86. Rales were heard at both bases. The heart was enlarged to the left and there was a crescendo apical diastolic murmur. The second pulmonic sound was accentuated. The liver was enlarged. Laryngoscopic examination revealed left recurrent nerve paralysis.

Laboratory Data: The ESR was 27 mm/hour. Hemogram, urine analysis and blood cultures were not remarkable. X-ray and fluoroscopy showed diffuse cardiac enlargement and congestive failure. There was left atrial enlargement and elevation of the left main bronchus. The ECG showed left ventricular hypertrophy.

Hospital Course: Low grade fever persisted for one week during which he received digitalis, ammonium chloride and penicillin. Blood cultures and laboratory tests remained normal. He was discharged feeling well but with slight dyspnea and persistent hoarseness. Diagnoses on discharge were rheumatic heart disease with mitral stenosis and left recurrent laryngeal nerve paralysis.

Second Admission (April 25 to May 29, 1952): Readmission was for increasing dyspnea, cough and left chest pain of three days' duration; he was still hoarse. Blood pressure was 132/80. There were a few basal rales, a grade II apical diastolic rumble was again heard and soft basal systolic and diastolic murmurs were noted for the first time. The spleen tip was palpable. ECG and x-ray were unchanged. The patient improved on bed rest and continued maintenance therapy and he was discharged with the diagnosis of mitral and aortic valvular disease.

Third Admission (August 18 to September 18, 1952): He again had increased dyspnea, but no pain. However, there were several episodes of hemoptysis. The spleen was transiently palpable. Blood and bone marrow cultures were negative. Maintenance therapy was continued and diseased teeth were extracted with penicillin coverage.

Fourth Hospitalization (December 15, 1952 to January 28, 1953): Because of several episodes of hemoptysis he was admitted to Boston Veterans Administration Hospital, where the apical diastolic murmur and a grade I apical systolic murmur were heard. Cardiac catheterization, for which he was referred to the Massachusetts General Hospital, revealed: resting cardiac index of 3.6 l/min/M^2; mean pulmonary artery pressure of 28 mm Hg; pulmonary wedge pressure of 24 mm at rest and 33 mm with exertion; calculated mitral valve area of 1.6 and 1.1 cm^2. He thereupon underwent a cardiotomy which revealed a normal mitral valve and marked left ventricular hypertrophy. The recurrent laryngeal nerve was found imbedded in a calcified node accounting for his hoarseness. No Aschoff bodies were noted in the left atrial appendage biopsy. Thereafter he recovered rapidly and was discharged on digitalis and salt restriction with the diagnosis of arteriosclerotic heart disease.

Fourth, Fifth and Sixth West Roxbury Admissions (between April 1953 and September 1954): He was admitted three times for recurrent congestive (predominantly left heart) failure. On each occasion the apical diastolic rumble was heard but the previously heard aortic murmurs were never again reported.

A phonocardiogram (Fig. 3) documented the presence of the apical diastolic murmur. The ECG showed

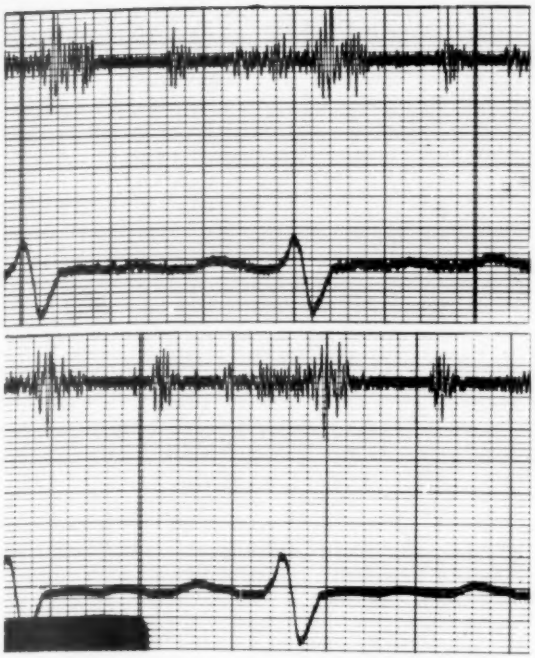

Fig. 3. Phonocardiogram and simultaneous electrocardiogram in case 2, showing deceptive presystolic murmur described in text.

first degree atrioventricular block and prolonged QRS time in addition to left ventricular hypertrophy and left atrial enlargement. BMR was plus 16 per cent. Radioactive iodine uptake was 37 per cent in 24 hr. Cholesterol was 265 mg/100 ml. A trial of cortisone (25 mg twice daily) in June, 1953 resulted in symptomatic improvement. He was considered to have "undiagnosed heart disease."

Seventh Hospitalization (September 28, 1954 to March 2, 1955): One month after his last discharge he appeared at the Detroit Veterans Administration Hospital complaining of dyspnea for two weeks and right chest pain for three days. Basal rales and dullness were noted. No apical diastolic murmur was heard but there was a grade II–III diastolic murmur in the third left intercostal space at the sternal border and a grade II apical systolic blow. The liver was down four fingers' breadth. ECG showed left ventricular hypertrophy and digitalis effect. He again underwent cardiac catheterization which disclosed: pulmonary wedge pressure 27 mm Hg; pulmonary artery pressure 46/28 (mean 36); radial artery pressure 111/69 (mean 81); cardiac output 4.63 *l*/min; cardiac index 2.47 *l*/min/M²; calculated mitral valve area 0.94 cm². This was interpreted as indicating mitral stenosis and he was subjected to thoracotomy. During induction of anesthesia he went into cardiac arrest which responded to massage. He thereafter deteriorated rapidly, dying 32 hours later.

Necropsy Data: The heart was strikingly enlarged, weighing 860 g with biventricular (especially left) hypertrophy. There were no significant abnormalities of the valves or coronary arteries. Microscopic examination confirmed this and disclosed myocardial hypertrophy with focal areas of degeneration and patchy fibrosis in the left ventricle. The kidneys and renal arterioles were not remarkable.

Comment: Except for the presence of left ventricular hypertrophy by ECG, this patient provided classic signs and symptoms of mitral stenosis, although (as is so frequently the case in genuine rheumatic disease) there was no history compatible with rheumatic fever. Auscultation of the "classic" mitral rumble and systolic blow was documented by phonocardiogram (Fig. 3). Cardiac catheterization by entirely separate teams seemed highly confirmatory. Cardiotomy, and later necropsy, revealed the deceptive nature of this seemingly perfect evidence. This case illustrates not only the pitfalls of physical diagnosis and physiological methods, but also the masquerading nature of idiopathic myocardial hypertrophy. Other investigators (q.v.) have reported similar deception.

Discussion

A search of the world literature disclosed 72 reports of patients with the isolated finding of unexplained large heart. Inasmuch as there has been no truly large series it was necessary, in order to define this syndrome adequately, to assemble the material from a multitude of sources. In view of its mysterious nature it was felt that, for descriptive purposes, fairly strict criteria should be employed not only for our own patients but also in selecting cases from reported series. Accordingly, cases were rejected because of insufficient corroborative data or of conflicting findings which might otherwise have been included.[1,2] Examples of the latter include active lues and aortic regurgitation,[3] advanced coronary arteriosclerosis,[4] possible glycogen storage disease,[5] extreme myocardial fibrosis,[6] aortic hypoplasia[7] and significant pre-existing hypertension.[2] Though the coexistence of idiopathic hypertrophy and another myocardial disease may occur, the present state of knowledge of the disorder necessitates its study in as pure form as possible.

One of the characteristics of idiopathic myocardial hypertrophy is the youth of its victims. Table II shows the ages at onset of symptoms of the 72 previously reported cases. Forty cases (56 per cent) were equally distributed between the third and fourth decades and fully 86 per cent occurred under the age of 50.

The typical course of this disease is one of increasing, usually intractable, congestive heart failure together with any of its usual complications, particularly pulmonary embolism. One is struck by its accelerated progress in most cases from a state of apparent well-being to irremediable decompensation. In 66 of the 72 reported cases sufficient data were at hand to permit a reasonable estimate of the survival of patients from symptomatic onset to death. In many cases, accuracy was facilitated by the relatively short, stormy course. Table III summarizes these data. Almost one-half (42 per cent) survived less than a year and 65 per cent were dead within two years of the time of onset.

TABLE II

Reported Cases of Idiopathic Myocardial Hypertrophy: Age at Onset of Symptoms

Age (decades)	Number of patients
10–19	5
20–29	20
30–39	20
40–49	17
50–59	8
60–69	2

TABLE III

Idiopathic Myocardial Hypertrophy: Survival from Onset of Symptoms in 66 Patients

Months	Number dead
0–6	17
7–12	11
13–18	7
19–24	7
25–30	2
31–36	5
37–42	4
43–48	2
Over 48	11

Postmortem examination disclosed that the single, often the only significant, lesion was myocardial hypertrophy principally of the left ventricle and to a lesser degree of the right. The coronary arteries were entirely free of lesions or had, at most, a few early atheromata; there was no evidence of valvular disease. Heart weights were available for 69 patients. That these were truly large hearts may be appreciated by reference to Table IV. The smallest, weighing 360 g, belonged to a woman. The largest weighed 1,475 g. It is apparent that the sizable majority (91 per cent) were in excess of 500 g; the mode (52 hearts) fell in the 450 to 650 g range.

TABLE IV

Idiopathic Myocardial Hypertrophy: Heart Weights in 69 Patients

Weight (g)	Number of Cases
350–399	1 (female)
400–449	5
450–499	10
500–549	12
550–599	10
600–649	10
650–699	4
700–749	9
750–799	2
800–849	4
850–899	1
Over 899	1 (1,475 g)

The foregoing considerations delineate the basic features of this syndrome: myocardial hypertrophy, forming the sole pathologic substrate for the progressive—usually rapid—evolution of heart failure, typically (but not invariably) occurring in young adults.

Levy[4] noted the clinical diagnosis of unexplained large heart 14 times out of 186,000 admissions in a 10-year period. It was pathologically confirmed five times out of 3,154 autopsies. Von Bonsdorff[8] saw nine cases in a consecutive autopsy series of 5,848 hearts.

Males have been the principal victims (58 out of 72 patients). The implication that there is an absolute predilection for Negroes[4,9,10] is not entirely correct. On the other hand, the data at hand would indicate that they are disproportionately affected. All of our own patients were Caucasians. However, of the 72 previously reported, 17 were Negroes. If one

subtracts the 13 foreign reports (emanating from countries with negligible Negro populations) the figures for the United States become more impressive, i.e., 42:17, or almost 30 per cent. This may, however, reflect the proportion of Negroes in the ward populations of the reporting institutions.

It is of some interest that, almost without exception, the reported victims of idiopathic myocardial hypertrophy were manual workers. Our eight patients were all in this category. One of the latter was a fish cutter and three were fishermen. It is noteworthy that these three were all of Portuguese extraction. Patients of Portuguese antecedents constitute well under 1 per cent of the admissions in our hospital.

Clinical Features

There is nothing specific in the clinical spectrum of idiopathic myocardial hypertrophy. Of 65 individual case reports recording a clear chief complaint, 46 list dyspnea of some type. However, five patients had abdominal pain,[12–14] three suffered from palpitations,[5,12,15] five had chest pain,[16–18] two had cough,[15] two had upper respiratory complaints,[19,20] and one each had edema (of face and ankles)[21] and right upper quadrant distress.[6] On the other hand, in no case did the underlying myocardial disease take long to declare itself. Two individuals in apparent good health died suddenly and were shown at necropsy to have this condition.[10,11] The others were hospitalized once or repeatedly for severe cardiac decompensation.

As in our own cases, a multitude of laboratory determinations—blood chemistries, hemograms, blood cultures and urine studies—were totally unrevealing. Chest films and fluoroscopy invariably showed generalized cardiac enlargement or left ventricular hypertrophy. Electrocardiographic patterns were interesting but equally nonspecific. Table V is a composite report of 92 tracings in 53 patients for whom adequate data were given. The arrhythmias noted would not be remarkable in type or number for any form of serious, decompensated heart disease. Nonspecific T wave changes were most frequent. Three records were read as showing myocardial infarction. Among the twenty-one with delayed ventricular conduction, fifteen were identified as left bundle branch block. The other six were not further described. Right bundle branch block has not been reported. Levy and von Glahn[12] observed that all their patients had abnormal electrocardiograms and that the degree of electrical abnormality was proportional to the amount of myocardial fibrosis noted later at autopsy.

TABLE V

Idiopathic Myocardial Hypertrophy: ECG Data.* Composite Results in 53 Cases (92 Tracings)

Nonspecific T wave abnormality		25
Delayed ventricular conduction		21
LBBB	15	
Intraventricular block	4	
"Bundle branch block"	2	
Arrhythmia		19
Supraventricular paroxysmal tachycardia	2	
Auricular fibrillation	12	
Auricular flutter	3	
"Junctional tachycardia"	2	
Auricular tachycardia	1	
Paroxysmal ventricular tachycardia	1	
Left ventricular hypertrophy or strain		10
Low-voltage QRS		10
Myocardial infarction		3
Right ventricular strain		1

* Exclusive of sinus tachycardia, digitalis effect, enlarged P waves and premature beats.

Lest it be proposed that hypertension had a role in the development of this lesion, it must be pointed out that the vast majority of cases had systolic pressures of 120 mm Hg or less and diastolic pressures between 80 and 90. The pulse pressure was thus usually small. Of course, these measurements were generally made when the patients were in florid congestive failure. The question of pre-existing hypertension, therefore, legitimately arises. This will be further dealt with in the discussion of etiology. Suffice it to say that retinopathy was not observed in these patients and absence of pathologic changes in the renal arterioles was a constant feature.

Embolism is especially frequent in this disease. Thirty-six cases (50 per cent) had emboli at

TABLE VI

Idiopathic Myocardial Hypertrophy: Sites of Embolization in 36 Cases with Proved Emboli

Pulmonary, total		34
Pulmonary only	19	
Pulmonary and systemic	15	
Systemic, total		23
Systemic only		
kidney	1	
brain	1	
Kidney, total		13
Spleen, total		4
Brain, total		4
Retina, total		2

autopsy. These are listed in Table VI. They were usually manifest antemortem, often being the terminal event. The overall total for pulmonary embolism, 34 patients, represents an autopsy incidence of 47 per cent; 17 patients (24 per cent) had one or more systemic emboli. Comparable autopsy series for myocardial infarction, for instance, have been pulmonary embolism in 23 per cent[22] and cerebral embolism in five—15 per cent.[23] This relatively high incidence in idiopathic myocardial hypertrophy may be related to the almost universal postmortem finding of mural thrombi affecting either the left ventricle or both ventricles.

Physical Findings

Of our patients, five had only soft apical systolic murmurs, two had no murmurs and one had the typical auscultatory findings of rheumatic mitral disease: an apical diastolic rumble and systolic blow. Of the reported cases, no murmurs were noted in 12, not mentioned in 22 and described in 38. The impressive majority (31) were soft apical systolic murmurs. However, there are four reports of apical systolic and diastolic murmurs [24,25] not otherwise qualified, and one each of presystolic rumble,[25] "variable systolic and diastolic"[25] and "loud mid-diastolic apical"[20] murmurs.

Certain other manifestations deserve at least passing mention. In 20 patients palpitation was a prominent complaint at some time, and the chief complaint in three. Twelve patients complained of some form of chest pain. As previously mentioned, sudden death claimed two persons in supposedly good health. In the others, sudden death in the course of management for congestive failure was fairly common, occurring in 19 (26 per cent) and was accounted for in three instances by pulmonary embolism. Fifteen patients developed some form of arrhythmia. One died during induction of anesthesia for pericardial surgery[9] and another had a ventricular arrhythmia. Autopsy in the remaining 14 patients failed to show an immediate cause of death; one may reasonably hypothecate physiologic deviations—e.g., ventricular arrhythmia— for these, too. One of the latter[15] was remarkable because of his record survival among known cases (96 months).

Pathologic Observations

Clinicopathologic studies of greatly hypertrophied hearts abound.[26–30] In most cases the etiology has been ascribed to coronary sclerosis, lues, rheumatic valvular disease or myocarditis. Where there had been no "obvious" cause for hypertrophy and the known blood pressure determinations had been within normal limits, the question of antecedent hypertension was raised.[24,25,27,30] The finding of renal and pancreatic arteriolar disease has been conceded to be evidence for this[31,32] and would rule out a case from the idiopathic group.

In addition to idiopathic hypertrophy, the reported cases commonly showed endocardial and mural thrombosis as well as varying degrees of mural and interstitial fibrosis. Many had foci of aseptic myocardial degeneration and necrosis, either restricted to or predominantly affecting the subendocardial zone. In none of these cases was a significant inflammatory reaction present or an infectious agent identified. Thus, we are not dealing with myocarditis.[9,20,33] On the other hand, the thrombi, degeneration and fibrosis are not specific. It has been postulated[4,34,35] that hypoxia and intraventricular stasis following decompensation result in subendocardial necrosis, producing endocardial thrombi and, subsequently, thebesian vein thrombosis. The latter is thought to precede and account for the foci and mural and subendocardial fibrosis. These, in turn, have been held to accentuate and aggravate the

changes initially causing them; in effect, a vicious cycle.

Diagnostic Considerations

Diagnosis is perhaps the most frustrating problem in idiopathic myocardial hypertrophy. As previously noted, anginal pain and highly "specific" murmurs can occur and lead the clinician to a diagnosis of coronary or valvular heart disease. Indeed, as our Case 2 reveals, even cardiac catheterization—by entirely separate teams—can "corroborate" a false mitral stenosis! The ECG can be read as myocardial infarction.[10,12,36] These are the fascinating minority of cases which suggest some of the formidable disguises of idiopathic myocardial hypertrophy. There remain the large majority with decompensated large hearts with or without nonspecific murmurs and electrocardiograms.

Previous investigators have differed somewhat on the chief differential diagnosis in these cases.[9,10,12,32,37] It was interesting, therefore, to note the sundry antemortem explanations given for 39 of the reported cases. (No separate antemortem diagnosis was mentioned in the other 33 cases). Table VII is a composite of the (often multiple) diagnoses in these patients. Of the 49 major diagnoses proposed, rheumatic heart disease was the most frequent,[9] even "silent mitral stenosis"[10] being invoked in the absence of a murmur. This was closely followed by myocarditis[8] of various types (q.v.). Indeed, this was the favorite diagnosis in our own cases (5 of 8). (Because of the looseness of its use, however, and because of the varied nomenclature of what we choose to call idiopathic myocardial hypertrophy, it is entirely possible that this condition was considered the equivalent of a myocarditis or its residuum. This may have represented a more etiological approach rather than a misdiagnosis.) In only seven instances was the unequivocally correct diagnosis made, the favorite term being "Idiopathic Cardiac Hypertrophy."[7,9,36,38] Five others were called heart disease of unknown etiology (or equivalent terms), which is at least a frank statement, and, like "myocarditis," perhaps indicating idiopathic myocardial hypertrophy. Myocardial infarction[3] has already been mentioned. Nine more bizarre diagnoses are also listed. (One might add others, e.g., amyloid and neoplastic heart disease, adult fibroelastosis and adult glycogen storage disease). If the composite is a valid sampling, the fact that arteriosclerotic or coronary heart disease was so little incriminated is a tribute to the perspicacity of the reporting clinicians or the youth of the patients.

TABLE VII

Composite of Antemortem Clinical Diagnoses in 72 Reported Cases of Idiopathic Myocardial Hypertrophy

No separate antemortem diagnosis stated: 33 patients		
Antemortem diagnosis stated: 39 patients		49 diagnoses
Rheumatic heart disease	9	
No valve specified		2
Carditis		2
Pericarditis		1
Pericarditis with effusion		1
Mitral stenosis		1
"Silent mitral stenosis"		1
Mitral stenosis and regurgitation; aortic stenosis and regurgitation		1
Myocarditis	8	
Chronic		5
"Myocarditis"		1
Acute nonspecific		1
Fiedler's		1
Arteriosclerotic heart disease (or equivalent)	7	
Idiopathic cardiac hypertrophy	7	
Heart disease of unknown etiology (or equivalent)	5	
Myocardial infarction	3	
Beriberi heart disease	2	

Other diagnoses: (1 case each): Hypertension; "Acute glomerulonephritis"; Constrictive pericarditis; Emphysema heart disease; Syphilitic aortitis; "Pericardial effusion"; "Dry pericarditis"; Interventricular septal defect.

Causal Hypotheses

The etiology of idiopathic myocardial hypertrophy is fertile ground for speculation. When defined strictly by the clinicopathologic criteria we have employed, it seems clear that evidence based on currently available methods would make this a more or less homogeneous group. The future may provide new technics which may

confirm and perhaps explain these cases. It is probable that progressive subdivision and identification will result in a diminishing proportion of truly idiopathic cause. Absence of a family history equally rules out familial cardiomegaly. We are not dealing with the very distinctive idiopathic hypertrophy of the right heart[40] which is largely a disease of females associated principally with right heart failure, cyanosis, pulmonary hypertension and ECG evidence of right ventricular strain with or without right atrial enlargement and right bundle branch block. Autopsy in these cases revealed predominantly right ventricular hypertrophy. Furthermore, it is probably the result of idiopathic pulmonary hypertension.[41] As far as present day histochemistry permits, diseases involving storage or infiltration of known foreign substances, e.g., amyloid, glycogen, are ruled out.

We have already disposed of pre-existing hypertension as a cause, bearing in mind that this, too, must be modified by dependence on available technics. Of about equal frequency in the minds of some investigators[15,25,32,36] is the notion that this is in fact a form of myocarditis or the residuum of pre-existing myocarditis. The absence at necropsy of primarily inflammatory changes would militate against the former. The contention that this is the result of myocarditis sometime in the past, either in the course of infectious disease[15,25,38] or as a primary entity[20,26,36] ranks with the idea of pre-existing hypertension. It can neither be proved nor entirely disproved and additionally involves all the difficulties of clinical diagnosis of myocarditis, let alone a retrospective myocarditis. In accord with this concept, it has been proposed that the influenza pandemic in 1918 was the remote cause of idiopathic myocardial hypertrophy appearing as late as the 1930's.[42] However, von Bonsdorff, reviewing "many hundreds of autopsies in influenza and grippe,"[25] considered this highly unlikely. It has been the often wide-spread patchy fibrosis in the absence of coronary disease which has largely influenced those favoring a post-myocarditic pathogenesis. In our pathologic discussion we have presented the most widely accepted mechanism for these patches, namely, thebesian vein thrombosis following intraventricular stasis during decompensation. Some have tendered the unsupported opinion that hypertrophy *per se* may result in fibrosis.[9]

In rats and hogs a potassium-deficient diet has caused myocardial lesions with necrosis and scarring in the absence of inflammation, but no relation could be established between this and idiopathic myocardial hypertrophy.[12] Similarly, Dock's early suggestion of vitamin B deficiency is unlikely;[36] the diagnosis of beriberi heart has been made and rejected following the failure of correction by thiamine. Perhaps the most bizarre suggestion is that of Laubry and Walser (1925)[14,43] who agreed that this is not a myocarditis, but believed the cause to lie in a "functional derangement of myocardial tonicity and contractility, perhaps mediated via nerves, endocrines or the physicochemical state of the blood". One may not agree with this omnibus suggestion, but there is no positive evidence to the contrary.

We are thus left only with a fair idea of what idiopathic myocardial hypertrophy is not. As long as this holds, the designation "idiopathic" is justified.

Nosologic Considerations

This syndrome has been reported under a variety of names. By far the most popular is some variant of "cardiac hypertrophy of unknown cause"[13,19,21,44,45] which is certainly descriptive and equivalent to our own choice, "idiopathic myocardial hypertrophy." However, there is an abundance of loose usage, the major fault of which is deceptive suggestion of the nature of this condition; for example, "myocarditis of unknown etiology,"[9] "myocardosis,"[2] "isolated interstitial myocarditis,"[8] "chronic fibroplastic myocarditis,"[15] "myocarditis perniciosa"[8] and others. Because of this, and for reasons of uniformity in communication, we propose "idiopathic myocardial hypertrophy" or equivalent terminology for these cases.

Summary

Idiopathic myocardial hypertrophy is a puzzling condition characterized by cardiac enlargement and progressive decompensation

occurring in previously healthy individuals. The sole pathologic finding is left ventricular hypertrophy with or without varying degrees of mural fibrosis. Valvular lesions are absent. The coronary arteries are widely patent and atheromata are either absent or insignificant.

Using strict criteria of selection, eight cases are reported and 72 cases are reviewed from the world literature. This disease is shown to affect mainly young adults. In most instances the course of the disorder is unusually rapid. Embolism is frequent and related to the common necropsy finding of mural and endocardial thrombi. No clinical or laboratory finding is of specific aid in diagnosis. Close simulation of specific lesions occasionally leads to mistaken diagnoses such as arteriosclerotic heart disease, mitral stenosis, etc.

The etiology of idiopathic myocardial hypertrophy remains obscure. It may represent one or more processes undetected by present technics. Various studies are cited which would invalidate the hypotheses of pre-existing hypertension, myocarditis or dietary deficiency as causative factors.

This condition should be considered in the differential diagnosis of congestive heart failure of unexplained origin.

Additional Case Histories

Case 3. A 49-year-old white male admitted in May and again in July, 1953 because of four years' swelling of the legs and increasing shortness of breath and paroxysmal nocturnal dyspnea. While in the Army in 1945 he was informed that he could be discharged on a medical basis because of heart findings; however, at that time he had been asymptomatic. Ten days before admission he had noted right upper quadrant pain on exertion. There had been no history of hemoptysis or chest pain; however, at the age of 16 he was said to have had rheumatic fever.

Physical examination revealed a tachycardia of 120, respiratory rate of 22, blood pressure 110/85 and temperature 98.0°. The ocular fundi were normal. There was minimal neck vein distention. Scattered basal inspiratory rales were noted on both sides. The left border of cardiac dullness was 13 cm from the midsternal line with a forceful apical impulse. There was a grade III harsh systolic murmur at the apex. The first mitral sound was not accentuated; $P_2 > A_2$. The liver was tender and enlarged. Moderate pitting ankle edema was noted. The initial white count was 15,600; hemoglobin was normal as was serology. Blood chemistries were within normal limits with the exception of NPN of 56. Chest x-ray showed cardiac enlargement with pulmonary vascular congestion and prominent pulmonary arteries as well as fluid at the left base. The ECG revealed first degree A-V block, incomplete left bundle branch block and auricular enlargement.

He had been on a program of low-salt diet, digitalis and diuretics. This was continued but his pulse remained elevated. On the third hospital day the temperature rose to 102° and he entered into a shock-like state. Because of the rapid downhill course he was started on cortisone acetate and given oxygen; a tentative diagnosis of pulmonary infarction had been made. On the sixth hospital day he complained of lower chest pain and right shoulder pain worse on respiration. His condition continued to deteriorate and he expired. Clinical diagnoses were (1) rheumatic valvulitis, inactive, with mitral insufficiency and cardiac decompensation; (2) pulmonary emboli, multiple.

Postmortem examination resulted in the following diagnoses: (1) idiopathic myocardial hypertrophy (650 g); (2) endocardial scarring, left ventricle, focal; (3) old thrombus, right auricular appendage; (4) pulmonary emboli, bilateral, with infarct of right lower lobe. There was no evidence of myocardial infarction. The coronary arteries were widely patent. All valves were normal.

Case 4. This was the first admission of this 56-year-old cotton mill laborer of Portuguese extraction whose chief complaint was shortness of breath. He gave a vague history of occasional substernal distress four years prior to admission but dated his present illness back three to four years when he began to have exertional dyspnea and cough. Within six months of onset of dyspnea he was admitted to a local hospital because of progressive shortness of breath, orthopnea, paroxysmal dyspnea and ankle edema. He responded rapidly to digitalis, low-sodium diet and monthly mercury injections but symptoms began to reappear a few months after discharge. One and again two years prior to admission he was admitted to other hospitals for congestive failure with good transient response to treatment. In the year prior to this admission he noted diminishing response to mercury and was unable to work. For three months he slept in a chair. His cough became worse and occasionally hemoptysis occurred. The past history and family history were entirely noncontributory.

Physical examination revealed a chronically ill, pale, perspiring, dyspneic and orthopneic white male. The blood pressure was 120/90, pulse rate 110, respiratory rate 20, and the temperature 98.6°. There were two fresh hemorrhages in the right ocular fundus. The neck veins were full at 45°. There were dullness and moist rales at both lung bases. The left border of cardiac dullness was in the left mid-axillary line in the sixth intercostal space. Frequent extrasystoles were heard. There were no thrills but there was a grade II apical systolic murmur and a loud presystolic gallop at the left sternal border; the second pulmonic sound was increased. The liver was down two fingers' breadth.

There was 3 plus edema of the ankles and legs. The venous pressure was 170 to 200 mm of water; circulation time 45 seconds. Vital capacity: total 1,200 cc, 1 second 1,000 cc. Urinalysis revealed 10 mg/100 ml albumin. The BUN was 44, and uric acid 8 mg/100 ml. Other laboratory values were within normal limits. X-rays showed increased vascularity of the lung fields and a large heart. There was fluid at the left base. Fluoroscopy showed left atrial prominence with the left cardiac border obscured by fluid. ECG revealed left bundle branch block and premature ventricular beats.

The patient was treated with a 200-mg sodium diet, digitalis, ammonium chloride, oxygen, mercuhydrin and sedatives. He developed hemoptysis and his fever spiked to 105.6°. Thoracentesis resulted in the removal of 400 cc of serosanguineous fluid from the left posterior chest. Because of the diagnosis of pulmonary embolism he had a bilateral femoral vein ligation but continued to have episodic extreme dyspnea and progressively rising pulse and respiratory rate. Eleven days after admission he became hypotensive and failed to respond to vasopressor therapy.

Autopsy revealed idiopathic hypertrophy of the heart (800 g), focal interstitial fibrosis of the myocardium and pulmonary infarctions. The coronary arteries were widely patent. The valves were all normal.

Case 5. This was the first admission of a 31-year-old married, white, male laborer who was well until 19 months prior to admission when he began to develop progressive exertional dyspnea relieved by rest. The chest film revealed an enlarged heart.

An ECG at another hospital showed left ventricular hypertrophy. He was treated with rest, digitalis, low-salt diet and mercuhydrin, with a 20-lb weight loss and moderate improvement. The working diagnosis at that time was idiopathic myocarditis. Since his discharge, however, congestive failure had persisted. Two weeks prior to admission there had been an irregular paroxysm of rapid heart action lasting one and a half hours. There was a two-month history of productive cough, worse in the week prior to admission.

The family history revealed that his mother died at age 49 of high blood pressure. His father died at 60 years of age of possible rheumatic heart disease. One sister died at the age of 29 of rheumatic heart disease. The patient's previous history revealed only recurrent tonsillitis up to four years prior to admission.

On physical examination he was slightly dyspneic with moderate venous distension in the neck. Temperature 99, pulse rate 100, blood pressure 150/90. There were coarse and fine rales at the right lung base. The heart was enlarged 5 cm to the left of the midclavicular line. There were irregular rhythm, a loud diastolic gallop, and a short, harsh apical systolic murmur. P_2 was greater than A_2. The liver was three fingers' breadth below the right costal margin and nontender. There were small shotty anterior cervical nodes. The hemogram was not remarkable. Urinalysis was within normal limits excepting for 20 to 30 white cells per high power field. Sputum culture revealed streptococcus pyogenes. Thymol turbidity 2.5 units, cephalin flocculation 3 plus. ESR was within normal limits as were fasting blood sugar, non-protein nitrogen and serum electrolytes.

X-ray of the chest showed cardiomegaly and increased vascular markings. There was a patch of increased density in the right lower lobe which was diagnosed as a penumonic process. Fluoroscopy revealed the heart to be tremendously enlarged; pulsations were good. Repeated electrocardiograms showed first degree A-V block, auricular enlargement and left ventricular hypertrophy. During his eight months' hospital course, the patient became progressively worse with intractable congestive failure. At his insistent request on several occasions he was sent out on leave of absence for several weeks only to return in more congestive failure. He died following a bout of ectopic auricular tachycardia.

Final clinical diagnoses were (1) myocarditis of unknown cause; (2) congestive heart failure; (3) apical paroxysmal tachycardia; (4) acute pulmonary edema.

Autopsy revealed idiopathic myocardial hypertrophy. Unfortunately the weight of the heart was omitted from the protocol; however, the heart was described as "very markedly enlarged." Organizing pneumonitis of the right lung and pulmonary arteriosclerosis were noted as well as chronic passive congestion of lungs, liver and spleen and bilateral hydrothorax. The valves and coronary arteries were normal.

Case 6. This was the first admission of this 32-year-old white male ship rigger evacuated from the Guam Naval Hospital three days before admission. Symptoms had begun eight weeks prior to admission with dyspnea and a sharp left chest pain exacerbated by breathing. One week later he was admitted to the Naval Hospital with temperature of 100° and a diagnosis of pleurisy. Several days later he had right upper quadrant tenderness and hepatomegaly with a tender liver. The electrocardiogram was then interpreted as "toxic myocarditis" and the diagnosis was changed to acute rheumatic fever. He became decompensated but responded to digitalis, oxygen, diuretics and aminophyllin. He was also treated with salicylates and vitamins. He had a second episode of congestive heart failure with response to the same treatment and the liver had receded above the costal margin. Fluoroscopy revealed normal heart size.

During his hospitalization on Guam he had a ventricular rate between 115 and 140. He had lost 40 lb. It was finally decided to evacuate him when the ventricular rate was 105. During the air journey he developed ankle edema and dyspnea.

The past case history revealed left lower lobe pneumonia in 1947. He had been in Europe during the second World War and was accustomed to drinking eight to nine beers nightly. The family history was not contributory.

Physical examination on admission revealed a well-developed, well-nourished, acutely ill white male.

There was questionable scleral and skin icterus. The lungs were clear. The heart was enlarged to the right of the sternum and to the left anterior axillary line. The sounds were muffled and there was an apical systolic blow and gallop rhythm. The pulse rate was 140, blood pressure 108/86. Peripheral pulses were good. The abdomen was slightly distended. The liver was down three fingers' breadth. The spleen tip was barely palpable. There was no edema. A fine macular rash was noted on the back. The circulation time was 30 seconds.

X-ray on admission revealed increased pulmonary markings. The heart was bottle-shaped with right and left enlargement. Fluoroscopy revealed weak pulsations suggesting pericardial effusion. Electrocardiogram on admission showed sinus tachycardia and low voltage throughout with prominent S_1, S_2 and Q_3. There was slight inversion of T_1 and T_2 and a low T_3. There was a prominent S in V_4, depressed ST in V_5, low T in V_4 and inverted T in V_5. The electrocardiogram was interpreted as consistent with myocarditis or pericarditis. Subsequent traces were essentially unchanged.

Laboratory examination was not remarkable excepting for a Van den Bergh of 2.4 (direct 1.8). Urine urobilinogen was positive in dilution of 1 to 10. During his hospitalization he was kept on maintenance digitoxin, ammonium chloride, mercuhydrin, a high-protein, high-calorie, low-sodium diet and 100 mg vitamin B_1 daily.

During the first few days he improved and had a six-lb diuresis. The right lower quadrant pain subsided in three to four days. The liver enlarged progressively to the umbilicus and icterus increased. Despite oxygen and continued therapy he pursued his downhill course with progressive pulmonary edema, punctuated by transient black cyanosis and finally coma on the day of death, 36 days following admission.

Autopsy revealed idiopathic myocardial hypertrophy (590 g), thrombus of the left ventricle, infarcts of the lungs, spleen and kidneys, pulmonary congestion and edema, hydropericardium (265 cc), ascites, cardiac cirrhosis of the liver, widely patent coronary vessels and normal heart valves.

Case 7. This was a white male laborer who had had six admissions between March 1947 and his final admission in March 1950 at which time he was 47 years old. During his initial admission in 1947 he had had multiple complaints including exertional dyspnea, low back pain and wasting of the left hand muscles. He had been well until November 1942 but two to three months after a 15-foot fall with back traumas he began to notice wasting of his left hand muscles. In January 1944 he began to have nonprogressive exertional dyspnea. There was no edema or orthopnea but occasional exertional palpitations. He had been in the Pacific theater during the war and was given 100 per cent disability for "coronary heart disease." Blood pressures during his first admission varied between 160/90 and 130/84. The neck veins were distended on recumbency. The lungs were clear. There was an enlarged heart on physical examination which was not confirmed on x-ray. Rhythm was always regular. There was a soft systolic blow at the apex and at the base. The spleen was down one to two fingers' breadth on inspiration. Atrophy of the left thenar eminence and interossei as well as the lumbricales was noted. Fluoroscopy revealed accentuated left and right heart borders. There was general cardiac enlargement with posterior displacement of the esophagus. Pulsations were weak and regular. The electrocardiogram showed idioventricular rhythm with ventricular rate of 42 to 50. P waves were not identifiable. The T was inverted in leads 2 and 3. There was a small R in CF_4 (2 mm), depressed ST and inverted T in CF_5. At that time diagnoses of progressive muscular atrophy (because of the wasting of left hand muscles) and interstitial myocarditis of unknown etiology were made.

His second admission, again in 1947, was for headaches. At this time his heart size was unchanged but there was moderate pulmonary congestion. The decholin circulation time was 35 sec and venous pressure 180 mm water (on exercise 350 mm). Digitalization produced no change. He was taken off digitalis. Subcutaneous adrenalin produced a slight increase in the ventricular rate but no P waves. Exercise produced the same effect. One-hundredth grain of atropine intravenously increased the ventricular rate to 84. Atropine plus adrenalin resulted in the same increase but no P waves were noted even with esophageal leads. He was released on a regimen of digitalis plus 40 minims of tincture of belladonna daily.

In January 1948 he was admitted for follow up. His condition was unchanged. Simultaneous apical stethogram was done with lead 1 and jugular pulse. There were normal first and second sounds with a soft systolic murmur. No P waves were noted. There was no A wave in the venogram.

He was readmitted 14 months later (December 4, 1949), again for re-evaluation, having been off digitalis for one month. He was subjectively and objectively unchanged but his main symptoms were exertional dyspnea and weakness. Blood pressure was 140/90, pulse 44. Vital capacity was 91 per cent of what had been predicted. It was felt that his heart had been unchanged in the $2^1/_2$ years of observation.

His final admission was between February and March 1950 at which time he was complaining of shortness of breadth and epigastric tightness. He was quite anxious and felt that he was not being treated satisfactorily with regard to his skeletal complaints. Blood pressure was 140/70, pulse 60. X-ray, fluoroscopy and electrocardiogram were still unchanged. He was treated for an anxiety reaction and discharged. Subsequent information revealed sudden death in 1951. No autopsy was obtained.

Comment: It was felt that in the absence of evidence of other etiologic types of heart disease this patient exhibited the clinical findings of idiopathic myocardial hypertrophy. This is the only unautopsied case that

we have been able to accept. We have been unable to find similar cardiac findings in other patients with the diagnosis of progressive muscular atrophy.

CASE 8. This was the first admission of a 26-year-old cook who entered with chief complaints of cough, vomiting and shortness of breath. He had been in excellent health until eight days prior to admission when he suddenly felt weak, had general malaise and later began coughing without production of sputum. There was at that time no pain or shortness of breath. Because of findings on electrocardiogram and chest film his physician suggested hospitalization which he at that time refused. Nevertheless, he was given 1.5 mg digitoxin in two days and 0.1 mg daily thereafter. Subsequently he felt somewhat better but continued to have some shortness of breath; there was no frank orthopnea or paroxysmal nocturnal dyspnea. On the day of admission he was again seen by the local doctor who insisted that he enter the hospital.

He did not have contact with any toxins. There was no history of diphtheria, tuberculosis or rheumatic fever. He did have scarlet fever in 1946 but no known sequellae. System review and family history were entirely noncontributory.

Physical examination on admission revealed a well developed, well nourished asthenic white male in no apparent distress. Temperature 98.6°, pulse 120, respirations 22, blood pressure 106/80. Other physical findings included moderate venous distention of the neck, some superficial venous dilatation on the chest, left cardiac border at the fifth interspace in the anterior axillary line. A distinct diastolic gallop was heard with occasional premature beats. There were no murmurs or thrills. P_2 was markedly greater than A_2. No masses or organs were palpable in the abdomen. A definite paradoxical pulse was palpable and could be recorded at a pressure of 108 systolic falling to 90 on inspiration. Admission laboratory data revealed a moderate leucocytosis (13,600) with normal differential, hematocrit 48, corrected sedimentation rate 9. Urinalysis was not remarkable nor were blood chemistries including liver function tests. Sputum, urine and blood cultures were negative. On chest x-ray and fluoroscopy the heart was enlarged in its transverse diameter with left ventricular prominence. The beat was rapid, irregular and weak with rippling motion especially in the auricular segment of the left cardiac border. The electrocardiogram on the night of admission was compatible with pericarditis or active myocardial disease. There was no significant change in subsequent cardiograms. During his hospital stay his temperature remained normal. The pulse varied between 100 and 130 and respirations were consistently 20 per min. His blood pressure varied between 90/70 and 110/80. Admission venous pressure was 215 mm of water, following which it was recorded at 230 mm of water and did not change from this figure. Decholin circulation time, which on admission was 28 sec, rose to 38 sec on the day before death.

He was continued on a program of digitalis, low-salt diet and diuretics and lost 16 lb. However, despite improvement, one week before demise he suddenly developed nausea, vomiting and severe tearing, substernal pain which radiated down both arms. This lasted for ten minutes and was relieved by morphine. He was started on cortisone and potassium chloride. The next day he felt much better and appeared better. However, there were no changes on physical or laboratory examination. He continued to have a diastolic gallop rhythm. The heart size did not change. At this time a working diagnosis of acute nonspecific myocarditis was made. Nine days after admission he had an episode of epigastric distress and vomiting with some precordial pain of less severity than the previous episode and again both physical examination and electrocardiogram revealed no significant change. The following morning his cortisone was increased to 500 mg daily. He improved somewhat following this but continued to have a diastolic gallop and paradoxical pulse. The heart size did not change. Eleven days following admission he had an episode of left chest pain. Because of clinical impression of pulmonary infarction anticoagulants were started. He was taken off antibiotics and steroids and continued on digitalis. However, he continued clinically in a precarious state with no sign of improvement and died on the eighteenth day. The final diagnosis was acute myocarditis of unknown cause.

Autopsy revealed idiopathic myocardial hypertrophy (500 g) with organizing mural thrombi in the left ventricle. There were miliary infarcts of the myocardium which were recent and thought to be embolic and old interstitial myocardial fibrosis which was focal and slight. There were fresh pulmonary infarcts in both lower lobes as well as pulmonary edema and congestion. The coronaries were widely patent and the heart valves were normal.

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Reports on Therapy

Treatment of Cardiac Arrhythmias with Hydroxyzine*

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THE SEARCH for effective, safe, anti-arrhythmic drugs continues despite the definite value of agents in general use today. This exploration is best explained and justified by two important clinical factors:

(1) The agents in clinical use have certain limitations relative to their effectiveness because of occasional, but definite serious side effects and toxicity.

(2) The essential diversity of the arrhythmias. The desirable goal of one universally effective, safe drug seems rather elusive when the varying etiologies and types of arrhythmias are considered. While many arrhythmias require no therapy because of their essentially benign or transient nature, other abnormal rhythms require rapid, effective treatment to preserve life.

Recently reported[1] animal pharmacologic studies interested us in hydroxyzine (Atarax®) as a drug for clinical trial in various arrhythmias. Since many agents, promising in animal screening tests, fail miserably in humans,[2] we approached this trial with guarded optimism. This paper reports on 50 patients treated with hydroxyzine.

MATERIAL AND METHODS

Patients selected from the medical service and medical clinic presented arrhythmias which required therapy. Hydroxyzine was given orally, intramuscularly or intravenously, depending on the exigency of the clinical situation. Oral medication was usually utilized for maintenance of the patient following initial parenteral therapy. Hydroxyzine was frequently tried after the failure of standard measures i.e. oxygen, sedatives, narcotics, barbiturates, procaine amide and quinidine. Electrocardiograms were taken prior to and following therapy. Many patients concurrently received maintenance doses of digitalis.

RESULTS

The results were excellent in 30 cases in which hydroxyzine restored and then maintained normal sinus rhythm. The drug had a good effect in six additional cases in which it either slowed the cardiac rate or decreased the frequency of extra systoles by at least 75 per cent. No significant beneficial effect was observed in the remaining 14 cases.

Table I summarizes the various arrhythmias treated and the results achieved in each type. Seven interesting case histories with illustrative electrocardiograms are presented.

CASE HISTORIES

CASE 5. E. J. H., a 67-year-old white female with several previous admissions for coronary artery disease, including one proven anterior wall myocardial infarction, entered the hospital with chest pain and shock. Her electrocardiogram showed paroxysmal ventricular tachycardia. Figure 1 shows the results of treatment with intravenous procaine amide and hydroxyzine.

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CASE 6. C. D., a 42-year-old white female, was admitted with frequent premature ventricular contractions, globus hystericus and hyperventilation syndrome. Her electrocardiogram revealed frequent ventricular extrasystoles. After 50 mg of hydroxyzine were given intramuscularly, the ventricular extrasystoles disappeared and normal sinus rhythm was maintained (Fig. 2).

CASE 7. T. B. C., a 73-year-old woman, had arteriosclerotic heart disease with frequent syncopal attacks and many premature ventricular contractions. She lost all her premature ventricular contractions after 24 hours of treatment with 25 mg of hydroxyzine orally three times daily (Fig. 3). She was maintained on this drug for approximately six months without any significant side effects.

CASE 8. L. H., a 69-year-old white female, was admitted with a diagnosis of coronary insufficiency resulting from very frequent premature ventricular contractions and occasional runs of bigeminy and trigeminy. She was placed on 25 mg of hydroxyzine orally four times daily with prompt elimination of premature ventricular contractions and disappearance of coronary insufficiency symptoms (Fig. 4).

CASE 40. A. N. B., a 66-year-old white male, was admitted with a typical acute anterior wall myocardial infarction and frequent multifocal ventricular premature contractions. Morphine and oxygen relieved his pain but the premature ventricular contractions persisted. He then received 50 mg of hydroxyzine intramuscularly 90 minutes after morphine. Within one hour the premature ventricular contractions were completely gone. He was then given 25 mg by mouth four times daily. Two days later digitalization was necessary. The ventricular

TABLE I

Summary of Results of Treatment with Hydroxyzine in 50 Patients with Cardiac Arrhythmias

Type of arrhythmia	Number of patients treated	Average dose and route of administration	Time interval from first dose to onset of effect (average)	Results		
				Excellent‡	Good§	Poor
Ventricular extrasystoles*	18	10–25 mg q.i.d. p.o. (50 mg I.M.)	Variable 1 hr to 24 hr	13	3	2
Auricular fibrillation	15	20–25 mg q.i.d. p.o.	24–36 hr	4	2‖	9
Paroxysmal tachycardias† (type unknown)	4	10–25 mg q.i.d. p.o.	Given prophylactically	3	1	0
Ventricular tachycardia	3	50–75–100 mg I.V.	Minutes	3	0	0
Wandering pacemaker with premature ventricular contractions	3	50–100 mg I.V.	30 min (1 case)	1	0	2
Paroxysmal auricular tachycardia	2	75 mg I.V. or 25 mg q.i.d. p.o.	8 min to several hr	2	0	0
Paroxysmal auricular fibrillation	2	50 mg p.o. or 50 mg I.M.	1 dose—within 1–2 hr	2	0	0
Auricular fibrillation with premature ventricular contractions	1	25 mg I.M. q4h	15 hr	1	0	0
Sinus tachycardia	1	75 mg I.V. 1 dose		0	0	1
Wolff-Parkinson-White syndrome with paroxysmal auricular tachycardia	1	25 mg q.i.d. p.o. down to b.i.d.	24 hr	1	0	0
TOTALS	50			30	6	14

* Often associated with other arrhythmias, such as bigeminy, trigeminy, bundle branch block—included are 3 cases of acute myocardial infarction.

† ECG's not available.

‡ Restored normal sinus rhythm.

§ Decreased extrasystoles at least 75 per cent.

‖ Rapid auricular fibrillation slowed.

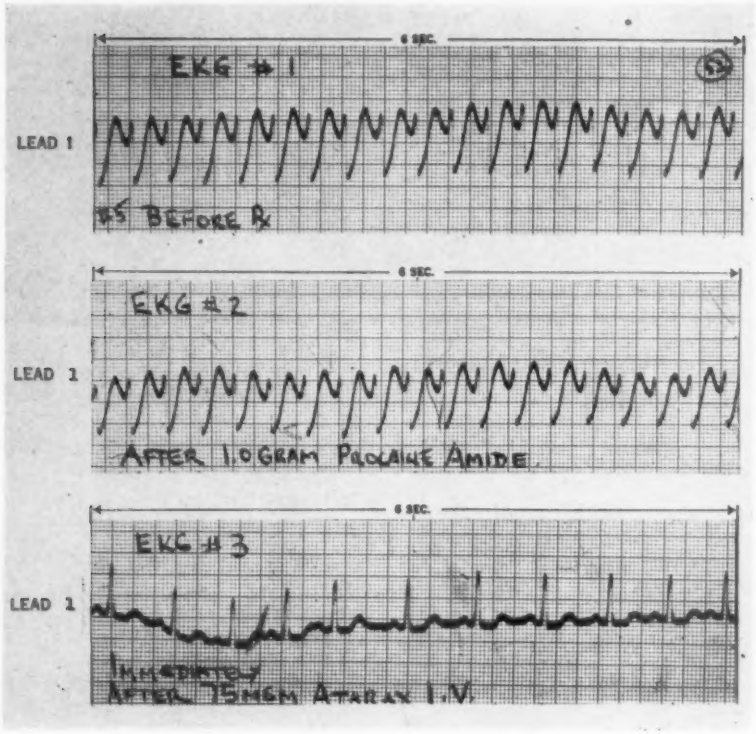

Fig. 1. Case 5. Top tracing shows paroxysmal ventricular tachycardia before any treatment. The middle tracing was taken after 1.0 g of procaine amide was administered intravenously. The bottom electrocardiogram shows the reversion to sinus rhythm immediately after the intravenous injection of 75 mg hydroxyzine.

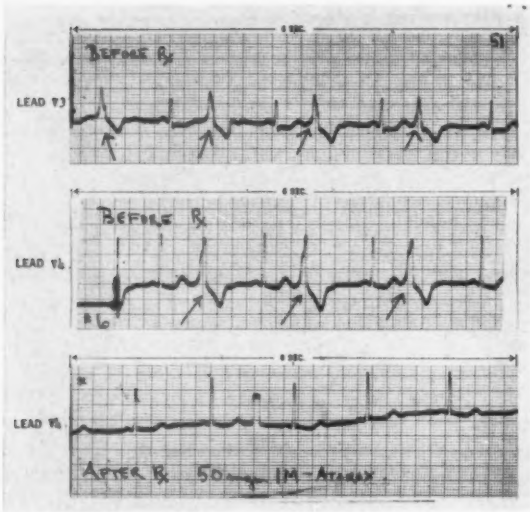

Fig. 2. Case 6. The top and middle electrocardiograms show sinus rhythm with frequent ventricular premature contractions causing bigeminal rhythm. In the bottom tracing 50 mg hydroxyzine intramuscularly have eliminated these ventricular premature contractions.

premature contractions were infrequent. The patient was maintained on hydroxyzine for six weeks (Fig. 5).

Case 42. C. P., a 52-year-old white woman with toxic nodular goiter, was hospitalized primarily for preoperative workup and control. She was known to have had auricular fibrillation for 18 months. When she was

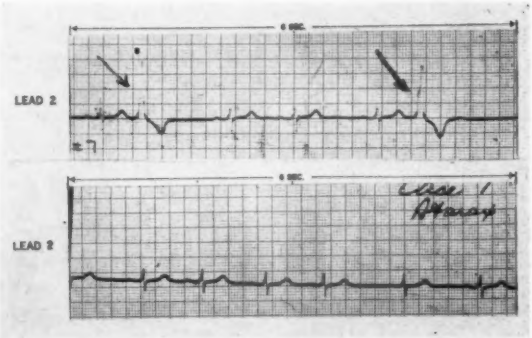

Fig. 3. Case 7. The upper tracing shows occasional premature ventricular contractions. After oral treatment with hydroxyzine, these extrasystoles have disappeared as shown in lower tracing.

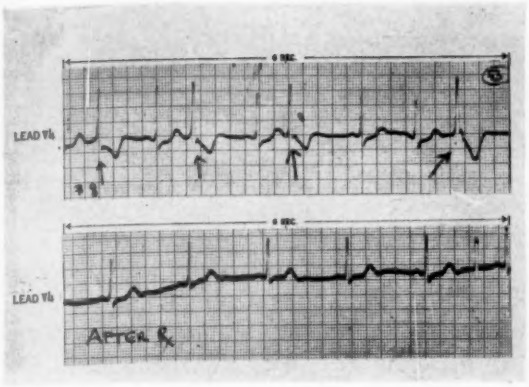

Fig. 4. Case 8. Upper tracing shows bigeminal rhythm due to frequent ventricular premature contractions. Lower tracing shows sinus rhythm after oral treatment with hydroxyzine.

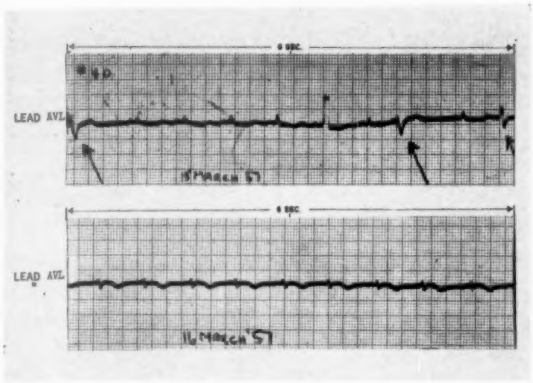

Fig. 5. Case 40. Occasional ventricular premature contractions shown in upper tracing disappear in lower lead after treatment with hydroxyzine orally.

placed on 25 mg of hydroxyzine orally four times daily without any other medication, she converted from auricular fibrillation to normal sinus rhythm on the third day and maintained regular sinus rhythm thereafter (Fig. 6). After one week she was started on an antithyroid drug as part of her preoperative medication.

CASE 43. O. S., a 50-year-old male, was admitted to the hospital with an acute anterior wall myocardial infarction with onset of pain 12 hours previously. His initial electrocardiogram showed multifocal ventricular extrasystoles and periods of bigeminy. Hydroxyzine 100 mg intramuscularly controlled the arrhythmia. Four hours later the rhythm was still regular (Fig. 7). He was then given 50 mg orally every six hours. Normal sinus rhythm was maintained for the next six weeks.

DISCUSSION

It soon became apparent that hydroxyzine was effective in treating acute arrhythmias, particularly those which disturbed ventricular

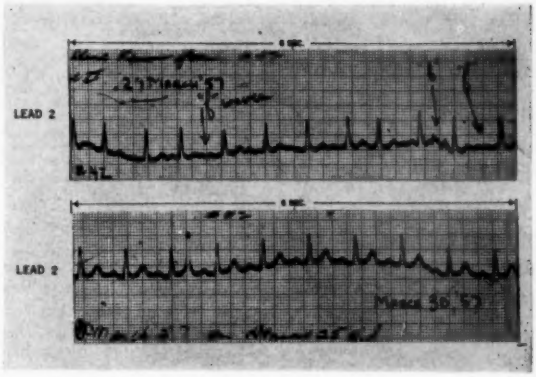

Fig. 6. Case 42. Upper tracing shows auricular fibrillation which reverted to sinus rhythm in lower tracing taken after oral treatment with hydroxyzine.

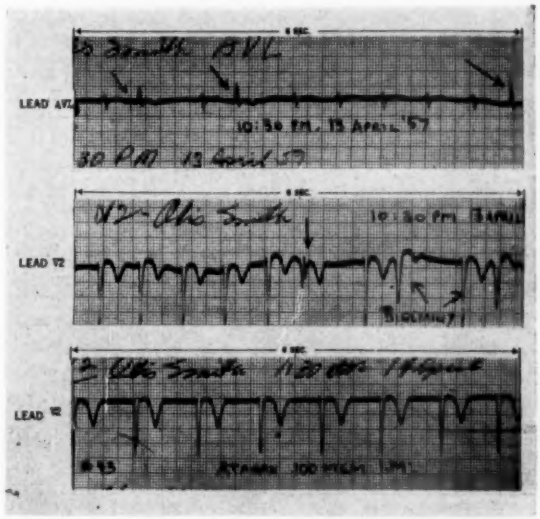

Fig. 7. Case 43. Frequent ventricular premature contractions shown in top and middle tracings disappear in the bottom lead taken after 100 mg hydroxyzine were given intramuscularly.

rhythm. The beneficial effects occurred most frequently in patients with ventricular extrasystoles, paroxysmal tachycardias, both auricular and ventricular, and in patients with ventricular extrasystoles complicating auricular fibrillation. Hydroxyzine did not seem to benefit auricular fibrillation, especially those cases which were of long standing duration. Nevertheless, auricular fibrillation was converted to normal sinus rhythm in four cases. Two of these were of recent onset.

The drug was generally unsuccessful in patients with long standing cardiac disease, in whom the myocardium and conduction system

were undoubtedly severely and chronically damaged.

While this agent was not uniformly effective in all situations, the number of good results is impressive. In addition to the beneficial effects, the drug is easily administered by any route, is free from toxicity, and generally has no untoward effects. This suggests to us that it is an excellent adjuvant to quinidine and procaine amide.

Hydroxyzine did not interfere with the concurrent use of digitalis or other medications.

The mechanism of action of hydroxyzine on cardiac rhythm is unknown. Further work is indicated to elucidate the sites and manner of action. Since hydroxyzine is an effective ataractic agent it might be supposed that the central nervous system is the primary site of action and the calming or sedative effect is the basis for restoring normal rhythm. We doubt this since many patients in this study were pre-treated with sedatives, barbiturates and narcotics with no effect on their cardiac rhythm. It seems that some direct myocardial effect occurred since in several patients normal sinus rhythm appeared either during the intravenous injection or within seconds thereafter.

The calming and tranquilizing abilities of hydroxyzine are of definite value and a desirable feature in the treatment of these patients with cardiac arrhythmias. In excessive doses, marked drowsiness was occasionally encountered which was easily alleviated by decreasing dosage. Mild drowsiness which occurred frequently was beneficial in the management of several patients with acute coronary occlusion, and in many severely anxious and fearful patients.

In some patients who were on anticoagulant therapy concurrently with hydroxyzine, the dosage requirement for the anticoagulant drug was markedly decreased. In some, satisfactory control of anticoagulant therapy could be obtained with about one-half the usual dosage. Patients on combined therapy should be observed closely and prothrombin time checked carefully.

Conclusions

(1) The use of hydroxyzine (atarax) was investigated in 50 patients with various cardiac arrhythmias.

(2) The results were excellent in 30 cases, the drug restored and then maintained normal sinus rhythm. Results were good in another six patients because the drug either definitely slowed the rapid rate or decreased the frequency of extrasystoles by at least 75 per cent.

(3) The arrhythmias most responsive to therapy with hydroxyzine were: (1) Ventricular extrasystoles; (2) auricular extrasystoles; (3) paroxysmal auricular tachycardia; (4) paroxysmal ventricular tachycardia.

(4) The drug was generally ineffective in the conversion of auricular fibrillation although four cases out of 16 were successfully converted.

(5) The drug was found safe, easily administered, and nontoxic in all cases. No untoward effects occurred in any patient when the drug was given either orally, intramuscularly or intravenously. This is a definite advantage over other agents in general use.

(6) Hydroxyzine is recommended for use in acute ventricular arrhythmias. Further work is indicated to establish its value as a prophylactic agent generally, and for prophylaxis in acute coronary occlusion and in preoperative preparation of patients.

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Quinidine Therapy for Atrial Fibrillation*

Indications and Toxic Effects

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QUINIDINE has been considered, since its introduction by Frey[1] in 1918, as the chief drug for the suppression of cardiac arrhythmias. Since that time quinidine therapy has been a subject of controversy as to whether the benefit from abolishing chronic cardiac arrhythmias and restoring normal sinus rhythm outweighs the risk of its toxic effects on the myocardium and respiratory center, and even of sudden death. The reason why quinidine fell into disrepute shortly after its introduction was due to the limited knowledge of its pharmacologic properties, and the lack of individual application.

The main purpose of this report is to present an unusual case of atrial fibrillation in which digitalis failed to control the ventricular rate, although there was no evidence of acute rheumatic activity, thyrotoxicosis, multiple pulmonary embolism, or Wolff-Parkinson-White syndrome. A situation arose where uncontrolled atrial fibrillation with a very rapid ventricular response caused intractable congestive heart failure with signs and symptoms of a shock-like state. In this desperate situation successful treatment with quinidine and conversion of atrial fibrillation to a normal sinus rhythm was lifesaving. However, this was complicated by marked sensitivity to quinidine with manifestations of severe quinidine toxicity in the electrocardiograms, which subsequently could have led to the death of the patient.

CASE HISTORY

The patient was an 18-year-old Puerto Rican high school student, who had had repeated episodes of rheumatic fever since the age of 9, despite prophylactic antibiotic therapy. In December 1954 he was admitted to the Mount Sinai Hospital because of increasing attacks of palpitations. He was found to have flutter-fibrillation and cardiac murmurs characteristic of mitral stenosis and insufficiency. The electrocardiogram showed atrial fibrillation with a ventricular rate of 150 beats per minute (Fig. 1). The absence of fever, a normal erythrocyte sedimentation rate (7 mm per hour), a normal C-reactive protein (0), and an antistreptolysin-O titer of 159 units, tended to rule out acute rheumatic activity as a cause of the atrial fibrillation. There was nothing in the history or physical examination to suggest thyrotoxicosis. An I^{131} uptake of 18 per cent ruled this out as a cause of the fibrillation.

Fig. 1. December 24, 1954. Record before start of quinidine therapy shows atrial fibrillation with rapid ventricular response averaging 140 beats per minute.

As the fibrillation was of recent onset it was decided to attempt conversion to normal sinus rhythm with quinidine. After digitalization with cedilanid, the patient was given increasing doses of quinidine. After he had received 0.6 g every two hours for four doses, toxicity was evidenced by tinnitus, widening of the QRS interval to 0.20 second, and runs of nodal and ventricular tachycardia superimposed on an atrial flutter with a 2:1 A-V response. Quinidine was discontinued and after 19 hours regular sinus rhythm was restored. Twenty-four hours later, the patient again reverted to atrial

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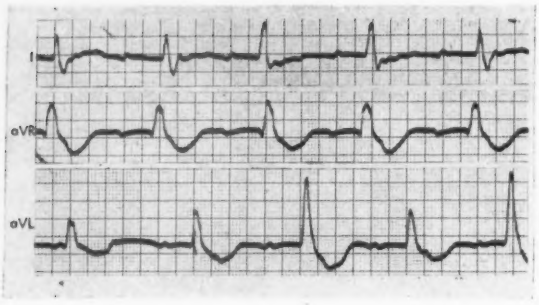

Fig. 2. March 21, 1955. Patient receiving 0.6 g quinidine sulfate orally every six hours. Complete atrioventricular block with idioventricular rhythm and ectopic atrial focus. P wave has different configuration than the normal one (see tracing following conversion to regular sinus rhythm). These changes suggest suppression of sinus node as well as A-V node.

fibrillation. As the patient seemed to be sensitive to quinidine it was decided to control the ventricular rate with digoxin. Although the patient's ventricular rate could be maintained around 85 beats per minute at rest, mild exercise would cause the ventricular rate to rise to about 120 beats per minute and produced severe fatigue and shortness of breath. Attempts to further increase the digitalis dose resulted in the appearance of multiple premature ventricular contractions. The patient was discharged in the hope that a spontaneous remission to normal rhythm would occur.

On March 7, 1955, one and one-half months after his previous discharge, the patient was readmitted because of palpitation, shortness of breath, and nausea. Although the normal temperature, sedimentation rate of 4 mm per hour, and a trace of C-reactive protein argued strongly against the presence of rheumatic activity, the patient was given 40 mg hydrocortisone three times a day to rule this out as a cause of the atrial fibrillation. After one week of therapy he had developed signs and symptoms of hypercorticism but there was no change in his cardiac rhythm.

Digitalis had been proved to be completely ineffectual in controlling the atrial filbrillation. The possibility of acute rheumatic activity had been excluded and there were no signs or symptoms suggesting pulmonary embolism or thyrotoxicosis as a cause for the intractable arrhythmia. Since the patient was rapidly going downhill, it was decided to allow the digitalis to become completely dissipated and to again attempt to convert him to regular sinus rhythm by careful use of quinidine; we hoped that this would improve his cardiac function and thus relieve his intractable congestive heart failure. Cortisone and gitaligin were discontinued and he was placed on complete bed rest. Five days later the electrocardiogram showed atrial fibrillation with a ventricular rate of 180 beats per min with no premature ventricular contractions. The patient had become lethargic and extremely short of breath. His extremities became cold and clammy and his blood pressure fell to 94/40. His urinary output decreased to 600 cc/day and his blood urea nitrogen rose from 14 mg/100 ml on admission to 36 mg/100 ml. He was then given 0.6 g of quinidine every six hours. After 36 hours, the patient showed signs of severe quinidine toxicity. He suffered tinnitus, anorexia, and nausea. The electrocardiograms showed prolongation of the QRS complex to 0.16 sec, depression of the S-A and A-V nodes and runs of ventricular tachycardia (Figs. 2, 3, 4). Quinidine was discontinued. One day later, the electrocardiogram revealed normal sinus rhythm with a QRS interval of 0.08 sec (Fig. 5). The patient became alert and was no longer short of breath. His extremities regained their warmth, the blood pressure returned to 100/70, and the urinary output rose to 4,690 cc during the 24 hours following conver-

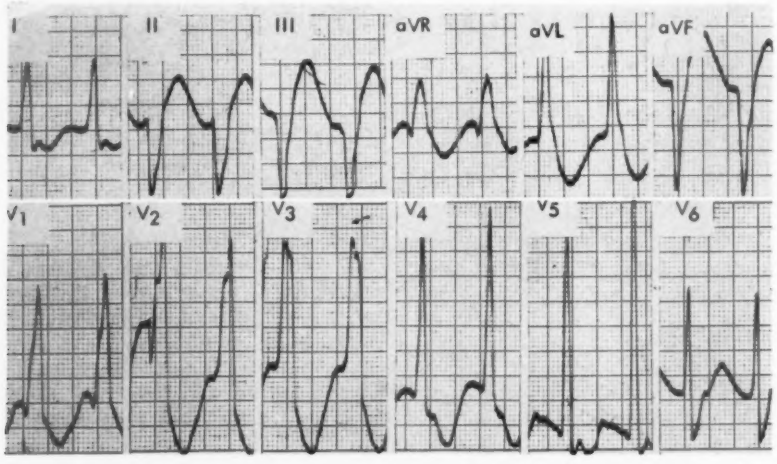

Fig. 3. March 22, 1955. Record during quinidine therapy shows right bundle branch block. Ventricular rate regular, averaging 120 beats per minute.

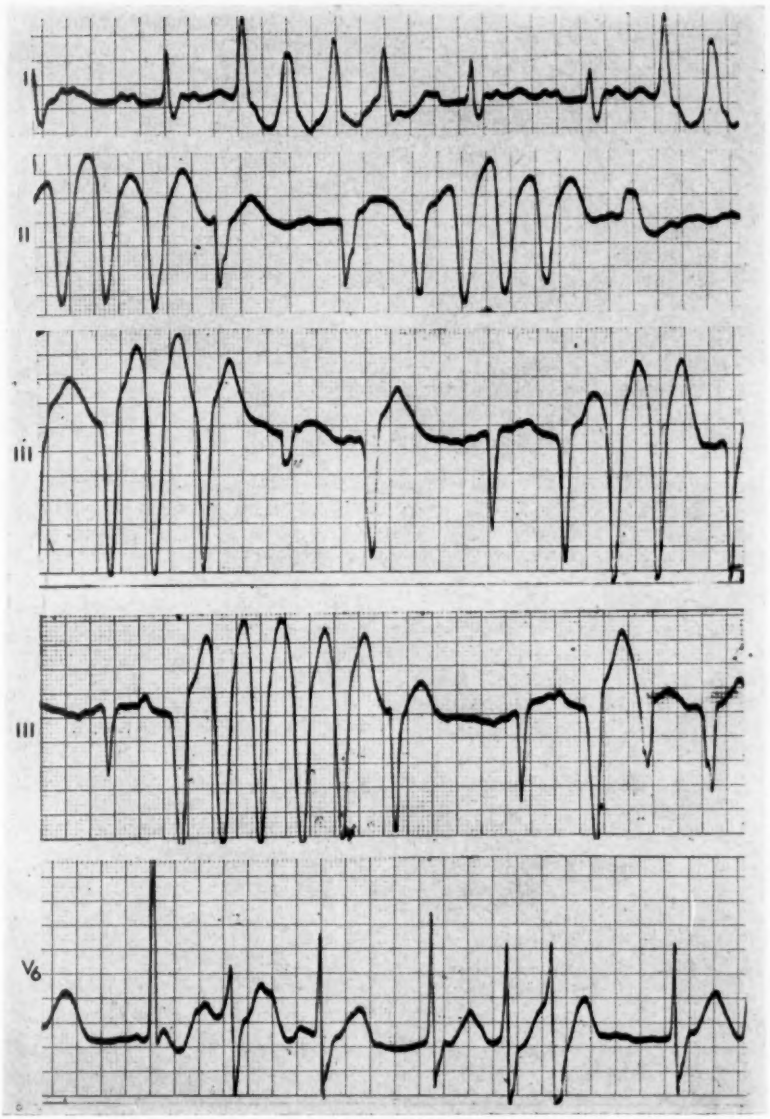

Fig. 4. March 22, 1955. Atrioventricular block with short bursts of ventricular tachycardia and multiple ventricular beats of multifocal origin.

sion to normal sinus rhythm. He was started on a maintenance regimen of 0.2 g quinidine every six hours and continued to have normal sinus rhythm for the next six days. Seven days after conversion he was again found to have atrial fibrillation with an apical rate of 140 beats per min. He was then given 0.6 g of quinidine every six hours. After three doses he again exhibited signs of quinidine toxicity in the electrocardiogram, with a widened QRS interval of 0.12 sec and many ventricular premature beats. He had no systemic complaints. Quinidine was discontinued. Twelve hours later when he was again found to have normal sinus rhythm, he was given a maintenance dose of 0.4 g of quinidine every six hours. After two weeks of observation he was discharged on this regimen. He had no palpitation of the heart or peripheral edema and could walk up three flights of stairs without getting short of breath.

During the succeeding nine months the patient was followed in the outpatient department. With the exception of a few transient relapses to atrial fibrillation he did well. He was maintained on quinidine therapy without the use of digitalis. He had no evidence of congestive heart failure, and was able to attend school and had an activity rating of class II according to the standards of the American Heart Association. On December 30, 1955, the patient was readmitted to the Mount Sinai

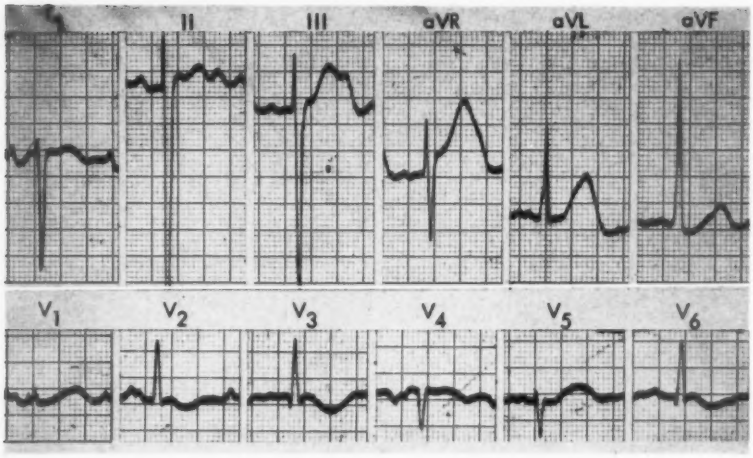

Fig. 5. March 23, 1955. Record after successful conversion of atrial fibrillation to regular sinus rhythm. P-R interval prolonged to 0.22 sec. Heart rate 85 beats per minute. Q-T interval prolonged. "Rolling" type of T waves which is characteristic for marked quinidine effect.

Hospital because of palpitations, dyspnea, peripheral edema and tinnitus of approximately five days' duration. The maintenance dose of quinidine was 0.5 g every six hours. An electrocardiogram showed the rhythm to be supraventricular tachycardia with a rate of about 100 beats per minute and periods of varying degrees of A-V block. Another strip showed right bundle branch block. It was the opinion of the attending staff that the patient had paroxysmal tachycardia, congestive heart failure and quinidine intoxication. It was decided to withhold all medication. On the day following this admission, a ventricular arrhythmia developed which was characterized by multifocal ventricular beats. The patient went into shock and died the afternoon of January 1, 1956.

Postmortem examination revealed rheumatic heart disease with massive cardiomegaly (weight, 680 g), severe mitral valvulitis producing mitral stenosis and insufficiency, and minimal valvulitis of the pulmonary, aortic and tricuspid valves. Microscopic examination of the heart confirmed the clinical impression that there was no active rheumatic carditis. There was evidence of healed subacute bacterial endocarditis involving the mitral valve, with old infarcts of kidney and spleen. Severe chronic passive congestion was noted with acute congestion of the liver. No evidence, either gross or microscopic, was present for hyperthyroidism or pulmonary emboli.

Discussion

Quinidine is used in prophylaxis and active treatment of patients with various ectopic rhythms. It is used in the treatment of premature contractions, either atrial, nodal, or ventricular; in paroxysmal atrial and nodal tachycardias, in atrial flutter and atrial fibrillation, and in ventricular tachycardia. A major indication is in the treatment of paroxysmal or established atrial fibrillation.

HAZARDS OF ATRIAL FIBRILLATION

The decision to use quinidine in atrial fibrillation must always be made with care. One must weigh the dangers of quinidine toxicity against the hazards associated with atrial fibrillation in each individual case before recommending this treatment. The hazards of atrial fibrillation are (1) the decrease in functional capacity of the heart; (2) embolic phenomena; (3) progressive cardiac enlargement which leads to congestive heart failure.

The Decrease in Functional Capacity of the Heart in Atrial Fibrillation: Many hemodynamic studies in experimental animals and man have shown that there is considerable impairment of the functional capacity of the heart and diminished cardiac reserve during atrial fibrillation, which markedly improve upon the return to regular sinus rhythm. Blumgart and Weiss[2] showed that the cardiac output and rate of blood flow were decreased during atrial fibrillation. Hecht,[3] using venous catheterization technics, found a decrease in cardiac output and a high arterio venous oxygen difference in patients with organic heart disease and atrial

fibrillation, whose heart rate was well controlled with digitalis and in whom there was no clinical evidence of congestive heart failure. Upon conversion of the fibrillation to sinus rhythm these changes returned to normal. They suggested that normally functioning atria aid in cardiac filling during periods of increased demands and that this reserve function is absent during atrial fibrillation.

Kory, Anderson, and Meneely,[4] employing cardiac catheterization, studied cardiac function at rest and after exercise in 34 patients with established atrial fibrillation and in three patients with recent or paroxysmal atrial fibrillation. Prior to conversion to normal sinus rhythm, the patients were treated with digitalis, diuretics, and salt restriction to achieve slow ventricular rates and maximum cardiac function. Following conversion to regular sinus rhythm with quinidine, the hemodynamic studies showed an increase in cardiac output in every patient, the mean increase being 43 ± 19 per cent at rest, and 39 ± 23 per cent with exercise. There was a proportionate increase in stroke volumes. Hansen, McClendon, and Kinsman[5] observed that following conversion to regular sinus rhythm there was a significant increase in cardiac output, a decrease in pulmonary blood volume, an increase in the rate of blood flow, lower venous pressure, and reduced right atrial pressure. These observations indicate that chronic atrial fibrillation despite full compensation and slow ventricular rate is accompanied by a low cardiac output, and that restoration to regular sinus rhythm is followed by a definite improvement in cardiac function at rest and in the response to exercise.

In the case report presented, in which there was severe congestive heart failure despite maximal therapy with digitalis, diuretics, and salt restriction, the persistent atrial fibrillation and rapid ventricular rate led to a shock-like state. Successful conversion to normal sinus rhythm with quinidine caused a dramatic improvement in the patient's condition. Most of the signs and symptoms of the advanced congestive heart failure disappeared. We can explain this best by assuming that a marked increase in cardiac output took place.

The Hazard of Embolism in Atrial Fibrillation: In several statistical surveys the cause of death in rheumatic heart disease due to emboli has varied from 10 to 20 per cent. Daley and co-workers[6] have shown that in 194 patients with rheumatic heart disease who had embolic episodes, mitral valve lesions were present in 97 per cent and atrial fibrillation in 90 per cent. Approximately 50 per cent of all emboli were cerebral in location with almost a 50 per cent mortality.

Progressive Cardiac Enlargement Leading Ultimately to Heart Failure in Atrial Fibrillation: In a study of 84 patients with atrial fibrillation of unknown etiology, Phillips and Levine[7] pointed out that atrial fibrillation may be the sole cause of cardiac dilatation and progressive heart failure even in patients with otherwise normal hearts.

FACTORS TO BE CONSIDERED IN QUINIDINE THERAPY

In deciding whether or not a patient with established atrial fibrillation should be converted to normal sinus rhythm the following factors should be considered:

(a) the likelihood that quinidine will restore normal rhythm;
(b) the untoward reactions during therapy;
(c) the likelihood of relapse with return to atrial fibrillation.

The Successful Restoration of Normal Rhythm with Quinidine: Conversion of atrial fibrillation to regular sinus rhythm has been reported to be successful in from 53 to 89 per cent of patients. The greatest success was obtained in those in whom atrial fibrillation persisted after the control of thyrotoxicosis. A long duration of fibrillation does not preclude conversion, but success is less likely in the presence of an enlarged heart or congestive heart failure.

The Untoward Reactions During Therapy: The hazards of therapy lie mainly in the toxic myocardial effect of the drug and in the complications that may follow the conversion to normal sinus rhythm. Quinidine therapy has been associated with sudden death. Fortunately, such catastrophies as respiratory collapse, circulatory collapse, and thrombocytopenic purpura are rare enough to be considered idiosyn-

crasies. The practice of observing the patient after giving him a small test dose helps to reduce this danger. The narrow therapeutic range of quinidine makes death via ventricular fibrillation an ever present danger. In our case, 0.4 g of quinidine was required every six hours to maintain normal sinus rhythm, while 0.6 g every six hours for only three doses produced marked toxicity manifested by prolongation of the QRS complex and ventricular tachycardia.

Toxic reactions to quinidine vary from patient to patient. Some workers (Sokolow[9,10] and Goldman[8]) have placed a great emphasis on blood serum levels of quinidine as a yardstick for dosage. However, because of great variations in recommended blood serum peak levels, it would not be safe and may even be dangerous to attain predetermined levels in all patients. According to Sokolow,[8,9] significant toxicity is infrequent at levels below 6 to 8 mg/*l* of plasma, but not infrequently successful conversion was obtained only with levels as high as from 10 to 15.8 mg/*l*. With such high levels the toxicity is markedly increased. From the practical point of view, taking electrocardiograms at frequent intervals, preferably before the administration of each dose, is simple and sufficiently safe.

The Likelihood of Relapse with Return to Atrial Fibrillation: Patients with atrial fibrillation on the basis of an enlarged left auricle due to mitral valve disease are generally difficult to convert to and maintain in normal sinus rhythm. A 20 to 49 per cent relapse rate within the first year following conversion has been reported in such cases. However, when faced with intractable congestive heart failure or repeated peripheral embolism threatening life, the clinician may elect to attempt quinidinization despite the added risk.

THE MODE OF ADMINISTRATION

A single oral dose of quinidine will exert the maximum cardiac effect in two hours and most of the effect will be dissipated in four hours.[12] When a given dose is administered every two hours, there will be a progressive increase in the blood level until the sixth dose, after which the rate of elimination equals approximately the rate of ingestion. It follows logically that during quinidinization there should be at least a two-hour interval between succeeding doses, and that the amount given each time should be increased at least every six doses if the rhythm is not converted to normal, provided there are no signs of toxicity. Five two-hour doses have been found to be the most effective, and 0.2 g has been recommended as the initial dose. However, as conversion or toxicity rarely occur at this level, many authors prefer to start with 0.4 g every two hours. Ideally, an electrocardiogram should be taken before each dose to detect early signs of toxicity. It should be noted that severe congestive heart failure and renal failure decrease the rate of quinidine elimination.

DIGITALIS IN THE TREATMENT OF ATRIAL FIBRILLATION WITH QUINIDINE

Goldman[8] and Sokolow,[9] in their respective large series, reported the appearance of atrial flutter in 70 per cent of the cases of atrial fibrillation during treatment with quinidine. As quinidinization is continued, the atrial flutter rate decreases before the patient's rhythm is converted to normal. This transition from atrial fibrillation to fast flutter to slow flutter allows more atrial stimuli to be conducted through the A-V node, thereby causing a rather sudden increase in the ventricular rate. This, in an already embarrassed myocardium, may result in clinical heart failure. Therefore, many clinicians choose to depress the A-V node by fully digitalizing their patients prior to quinidinization and keeping them on maintenance dosage of digitalis until they are converted to normal sinus rhythm. Care must be taken to avoid overdigitalization, as complete A-V block due to digitalis added to ventricular myocardial depression caused by quinidine may result in asystole and sudden death.[11]

The fibrillating heart is not a fully compensated one. It is less efficient than one beating regularly. The administration of cardiac depressants to an already embarrassed myocardium may aggravate the condition. Therefore, it may be wise to restore the heart muscle to the optimum physiological state by digitalization before quinidine therapy is started. Once the heart is fully digitalized, quinidine therapy is then begun, with the patient on a maintenance

dose of digitalis. Slowing of the heart rate and dimininishing heart failure will make the heart more responsive to quinidine and lessen the danger of toxic reactions.

ELECTROCARDIOGRAPHIC CHANGES FOLLOWING TREATMENT WITH QUINIDINE

We had the opportunity in the case presented to observe the changes which quinidine can produce in all components of the electrocardiogram. The earliest electrocardiographic change observed is the prolongation of the Q-T interval (Fig. 5). This lengthening is within the therapeutic range unless the prolongation is marked. At the time of maximal action the absolute Q-T duration may show an increase of about 0.013 sec for each 0.1 g of quinidine sulfate.[13] The P waves, if present, are widened and notched; T waves are flattened with typical widening of their summit, and later are even inverted and the S-T segment is depressed. After the prolonged use of quinidine, a very typical "rolling" T wave may be observed (Fig. 5) and RS-T segment may be depressed. The P, RS-T, Q-T, and T changes are within the therapeutic range.

A marked increase of the QRS interval of over 25 per cent is probably the best evidence of toxicity (Fig. 2). An increase of over 50 per cent in the width of the QRS complex is hazardous, and may be associated with such serious ectopic rhythms as ventricular tachycardia (Fig. 3) and ventricular fibrillation (Fig. 4). With the widening of the QRS complex a typical bundle branch block may appear (Figs. 2 and 3) which may be premonitory to the development of ventricular tachycardia.[14] Therefore, it would appear to be good practice to withhold further doses of quinidine after the QRS is prolonged from 25 to 50 per cent or more than 0.12 to 0.14 sec.[15] In the great majority of reported cases in which there was a marked prolongation of the QRS complex, the original QRS duration was re-established within 24 hours after the cessation of treatment.

INDICATIONS AND CONTRAINDICATIONS FOR QUINIDINE THERAPY

After consideration of the hazards of atrial fibrillation and the above-enumerated factors in treatment, the most important question still remains to be answered, namely, who are the best candidates for this therapy. The following types of patients are considered good candidates for quinidine therapy:

(1) Patients with paroxysmal atrial fibrillation without other evidence of heart disease.

(2) Patients with thyrotoxicosis and atrial fibrillation which persists after they have been made euthyroid (by means of either surgery or radioactive iodine).

(3) Patients with repeated embolism from atrial mural thrombosis, especially if mitral valvulotomy cannot be performed. Conversion is usually attempted after a period of anticoagulant therapy to permit organization of the thrombus.

(4) Patients with intractable congestive heart failure which cannot be controlled adequately with digitalis, mercurials, bed rest and sodium-restricted diets deserve an attempt at conversion of their atrial fibrillation to regular sinus rhythm in spite of all risks. It is our opinion that these cases are candidates for quinidine therapy in view of the 31 to 43 per cent expected increase in cardiac output obtainable by conversion.

Quinidine treatment is contraindicated in patients with an intraventricular conduction defect or atrioventricular block. Such patients should not be treated with quinidine as asystole may result when a myocardial depressant is used in the presence of already depressed junctional tissue.[11]

Summary

We have presented a case of atrial fibrillation not due to acute rheumatic activity, thyrotoxicosis, multiple pulmonary emboli, or Wolff-Parkinson-White disease, in which digitalis failed to control the ventricular rate and in which conversion to normal sinus rhythm with quinidine proved to be lifesaving. However, this was accompanied by signs and symptoms of severe quinidine toxicity. The taking of frequent electrocardiograms as a guide to dosage during quinidinization was stressed.

The fact that the increase in cardiac output obtained by conversion of atrial fibrillation to normal sinus rhythm may be lifesaving in cases

of intractable congestive heart failure is re-emphasized.

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Severe Case of Ventricular Tachycardia

Treatment with Intravenous Quinidine

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THE FOLLOWING case of ventricular tachycardia is reported because of the unusual severity of symptoms and the lack of response to established therapy.

CASE HISTORY

A female, 68 years old, was admitted to the Adelphi Hospital by Dr. Egon Feldman. For about six months previous to admission she experienced some precordial pain from time to time, occurring on exertion. During the night previous to admission she suddenly developed palpitation and fainting sensation. She was found to have marked tachycardia, and was given 6 gr of quinidine orally. On admission to the hospital the following morning, she presented moderate pallor and slight cyanosis. Mentally, she was alert, fully conscious of her environment, and had no undue complaints, except for some "fluttering" in the chest and marked weakness. The heart rate was 190 beats per minute and the heart sounds were of poor quality. The pulse was hardly perceptible and the blood pressure was 70 systolic and 50 diastolic.

She was placed under oxygen and quinidine sulphate was ordered, in doses of 6 gr every hour to be given by mouth until the rhythm was restored to normal. After five hours the tachycardia still persisted. The rate came down to about 170 per min and the intraventricular conduction time became more prolonged. For fear of the onset of possible ventricular fibrillation, the same dose of quinidine was ordered to be given every four hours. The tachycardia persisted. The blood pressure was at times unobtainable, at other times it varied between 60 and 80 systolic and 0 to 40 diastolic. The pulse was frequently imperceptible.

On the second day of admission the tachycardia still persisted and she showed more profound shock with cold, clammy perspiration, nausea and recurring vomiting. She then received pronestyl, one gram intravenously, followed by 250 mg every four hours by mouth. There was no response to this medication after 12 hours. In view of progressive increase in the intensity of shock, it was decided to give her levophed bitartarate, 4 cc per 1,000 cc of 5 per cent glucose solution, by slow intravenous drip. No effect was produced either in raising the blood pressure or in change in the heart rhythm. Quinidine hydrochloride intramuscularly was then tried, in doses of 6 gr every four hours. The tachycardia continued without interruption and shock became more profound. On the third day of admission, atabrine was tried in doses of 0.3 mg every two hours, but no effect was noticed after 10 hours and the drug was discontinued. The use of quinidine intramuscularly was resumed.

On the fourth day the shock became most profound. The pulse and blood pressure were mostly unobtainable and the ventricular rate was 195. The patient was extremely restless and hard to control, at times irrational. Dyspnea and cyanosis became marked. A cold, clammy sweat covered her body, and an early fatal outcome was expected. Believing that very little of the quinidine when given by mouth or intramuscularly was absorbed due to the circulatory stasis, and in view of the desperate condition, a 5 cc vial of 9 gr of quinidine hydrochloride was given intravenously in full concentration. Transient respiratory standstill with profound cyanosis occurred but soon respiration was resumed and the heart rhythm returned to a normal sinus mechanism, with a rate of about 72 per min. The pulse became perceptible and the blood pressure rose to 108 systolic and 70 diastolic. The condition progressively improved. The pulse soon assumed a normal quality and the blood pressure increased to 120 systolic and 80 diastolic at the end of the day. Maintenance doses of 3 gr of quinidine sulfate by mouth were given every four hours. In six days the patient was out of bed and at the end of two weeks she left the hospital in excellent condition.

Laboratory Findings: The highest temperature during her stay in the hospital was 100.5 F. The laboratory findings on the day of admission were: urine, 1 plus albumin and casts, occasional red and white blood cell; blood count, hemoglobin 13.5 g (87 per cent), white blood cells 14,350, with a differential of 78 per cent neutrophiles, 2 per cent bands, 18 per cent lymphocytes, and 2 per cent monocytes. The blood cell sedimentation rate was 36 mm in one hour and hematocrit 43 per cent; blood urea nitrogen 66 mg and sugar 210 mg per 100 cc. One day after the restoration of the normal rhythm the blood count showed hemoglobin 12 g (77 per cent), white cells 12,550 with 77 per cent neutro-

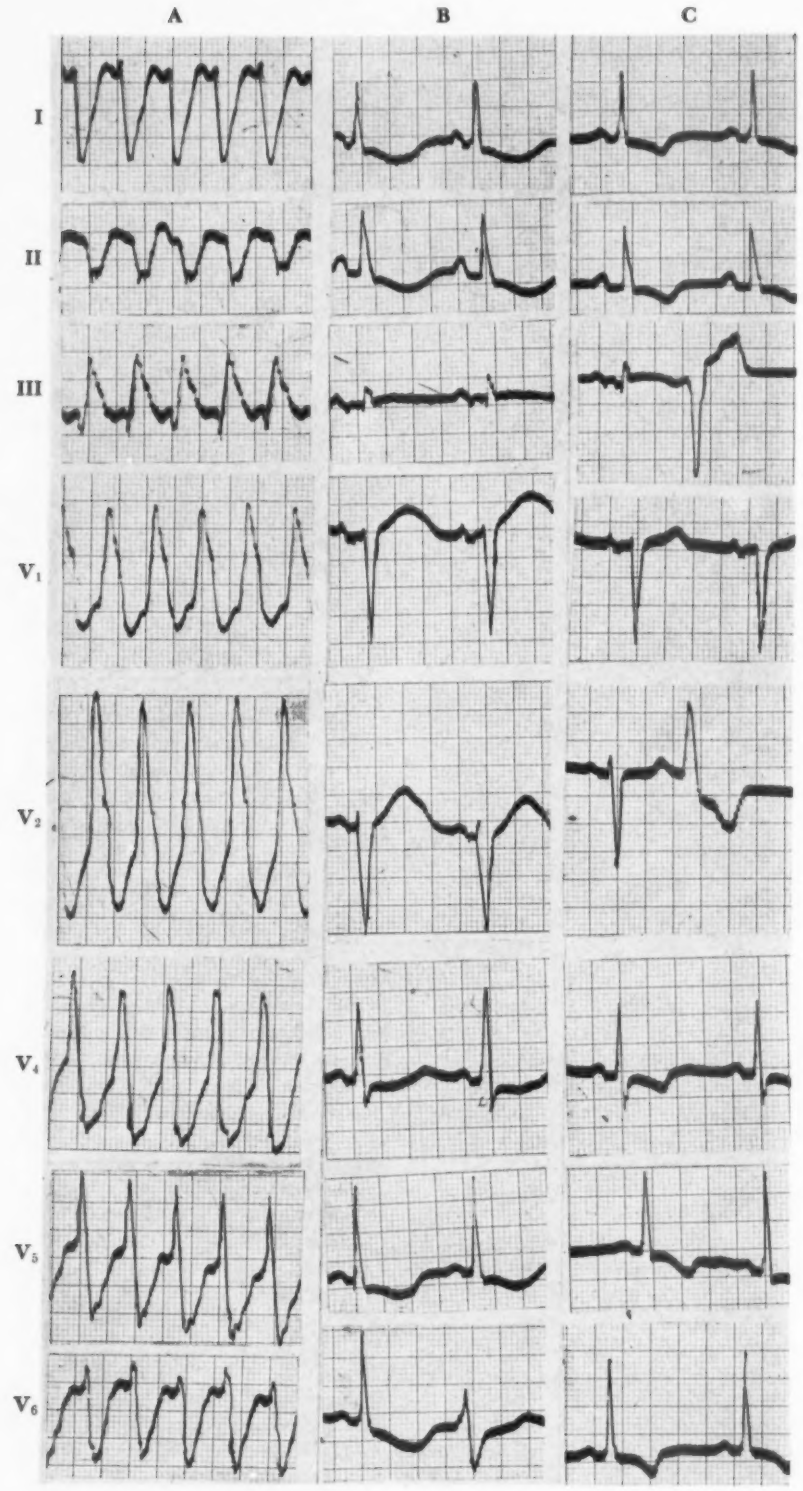

Fig. 1. (A). Ventricular tachycardia, rate 175 per min (B). One hour after reversion to normal sinus rhythm. Prolonged Q-T interval due to quinidine effect. (C). One week later. Q-T interval normal.

philes, 20 per cent lymphocytes, and 3 per cent mononuclear cells. The hematocrit was 39 per cent and the sedimentation rate 32 mm in one hour. The blood sugar was 100 mg and the urea nitrogen 36.6 mg per 100 cc. Four days after the restoration of the normal rhythm the blood urea nitrogen was 13 mg.

ECG Findings: Many electrocardiograms were obtained during the attack and subsequently, of which the accompanying three are representative (Fig. 1). *Tracing A* was obtained soon after admission. It shows ectopic tachycardia originating in the left ventricle. The rate is 175 per min. Subsequent tracings obtained at intervals of six to twelve hours showed practically the same findings except for an increase or a decrease in rate from time to time. The highest rate was 190 and the lowest 168. During the lower rates the intraventricular conduction was more prolonged.

Tracing B was obtained on the fourth day, one hour after normal sinus rhythm was restored. The outstanding feature is the prolonged Q-T interval which approximates 0.57 sec with slow slope, shallow negativity, and rounding of the T wave in leads 1, 2, V_5 and V_6, with corresponding rounding of the positive T wave in lead V_1. These changes are due to quinidine therapy. One ventricular premature contraction is seen in lead V_6, having its origin in the left ventricle, as in the paroxysmal tachycardia.

Tracing C, obtained one week later, shows the patterns of left ventricular strain and subendocardial myocardial ischemia of the anterolateral wall of the left ventricle. One ectopic contraction is seen in lead 3, originating in the right ventricle. Another ectopic contraction is seen in lead V_2, originating in the left ventricle. The Q-T interval is now about 0.39 sec, which is within normal limits and the T wave is no longer rounded, indicating the subsidence of the quinidine effect.

Comments

It is not intended here to advocate the intravenous use of qunidine in all cases of ventricular tachycardia. Trial should be had of quinidine by mouth, to which most cases respond. We feel, however, that where there is profound shock with severe circulatory failure, the amount of quinidine absorbed when given by mouth or by intramuscular injection is small, and may have no effect on the heart. In such cases, quinidine given by intravenous route in concentrated form may result in immediate response not obtained when given by other methods.

Clagett[1] advocates the use of quinidine lactate by diluting a 10 cc ampule, containing 0.65 g of the drug in 50 cc of 5 per cent glucose solution, and giving it by slow intravenous infusion at the rate of 2 cc per min in most cases of ectopic ventricular tachycardia. He considers this method preferable to the intramuscular route, as it can be more easily controlled. He feels that deaths attributable by some authors to quinidine therapy are in many cases actually caused by the tachycardia. We agree with his views, but we feel that in desperate cases, such as the one reported here, quinidine should be given in a more concentrated form. January and coworkers[2] likewise advocated the intravenous use of this drug, which they found safe and which produced prompt control of the attack.

The hyperglycemia and azotemia observed in this case during the attack were caused of course by the profound shock. Both returned to normal with recovery—the hyperglycemia first.

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Case Reports

Escape-Capture Bigeminy

Report of a Case of A-V Dissociation Initiated by 2:1 S-A Block with Resulting Bigeminal Rhythm*

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TWO-TO-ONE S-A block is not common and A-V dissociation released by such block is obviously less so. When bigeminal rhythm, of so-called "pseudoreciprocal" type, is a by-product of this unusual combination, the resulting triple alliance is indeed a rarity. Our purpose is to present one such rara avis and to question the adequacy of existing terminology.

CASE HISTORY

The patient was a 56-year-old white man admitted to the Mercy Hospital complaining of anorexia, shortness of breath, abdominal distension, edema of ankles, orthopnea and nocturia of two months' duration. Physical examination revealed well marked signs of congestive heart failure. Blood urea, serum potassium and chloride were normal; serum sodium was 125 meq per liter. He was a known mild diabetic and the cause of his myocardial failure was thought to be coronary disease. For the past three years he had been maintained on 0.1 mg digitoxin daily.

DISCUSSION OF ELECTROCARDIOGRAMS

The electrocardiogram on admission (Fig. 1 and 2A) showed a sinus rate of 27–28 with A-V dissociation. Ventricles were under control of the A-V node, whose inherent rate was 35–40. Runs of bigeminy, consisting of two to four consecutive pairs, were interrupted only by single unpaired beats. Of the paired beats the first was always a nodal escape beat and the second a conducted sinus beat (ventricular capture).

Three other phenomena in Figure 1 deserve passing mention: (1) Ventricular aberration of right bundle branch block type usually characterized the earlier conducted beats (when ventricular activation began within 0.62 sec after the onset of the preceding ventricular impulse). (2) An inverse R-P/P-R ratio within the bigeminal groups was evident—the shorter the R-P interval the longer the contiguous P-R interval and vice versa. Both of these findings are, of course, well recognized accompaniments of ventricular capture beats. (3) A marked sinus allorhythmia consistently recurred throughout the tracing, so that the P waves terminating the shortest P-P intervals always coincided with the isolated escape beats. Indeed it was clearly this phasic sinus acceleration that put an end to each brief series of coupled beats.

Digitoxin was discontinued. Six days later another electrocardiogram showed a prevailing sinus rhythm with a rate of 54–55, or exactly double the previously observed rate. This doubling of atrial rate alone suggested that the mechanism of the previous marked bradycardia was 2:1 S-A block. This impression was substantiated by the occasional appearance of sinus pauses equal to exactly double the then dominant P-P interval (Fig. 2B). These findings threw retrospective light on the underlying mechanism of the previous A-V dissociation—presumably a persistent 2:1 S-A block had

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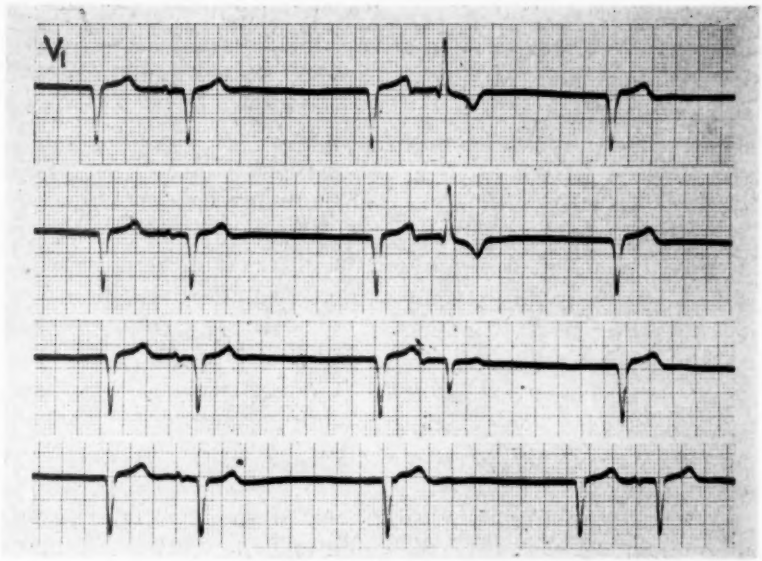

Fig. 1. The four strips form a continuous tracing. In the top strip the first beat is a nodal escape beat; this is followed by a conducted sinus beat (ventricular capture). The next couplet is similar except that, as the sinus beat occurs earlier after the escape beat, the conducted beat shows ventricular aberration. Then comes a lone escape beat with the next P wave buried in its ascending limb. Similar sequences are then repeated. Note the sinus allorhythmia: consecutive P-P intervals measure 211, 180, 225, 213, 182, 223, 214, 179, 224, 186 and 212 hundredths of a second.

allowed the A-V node to escape and initiate a period of prolonged A-V dissociation.

Four days later a third electrocardiogram showed even more numerous sinus pauses although no further digitalis had been administered. When these pauses occurred consecutively, A-V dissociation with short runs of bigeminy resulted, each pair again consisting of a nodal escape beat followed by a conducted sinus beat.

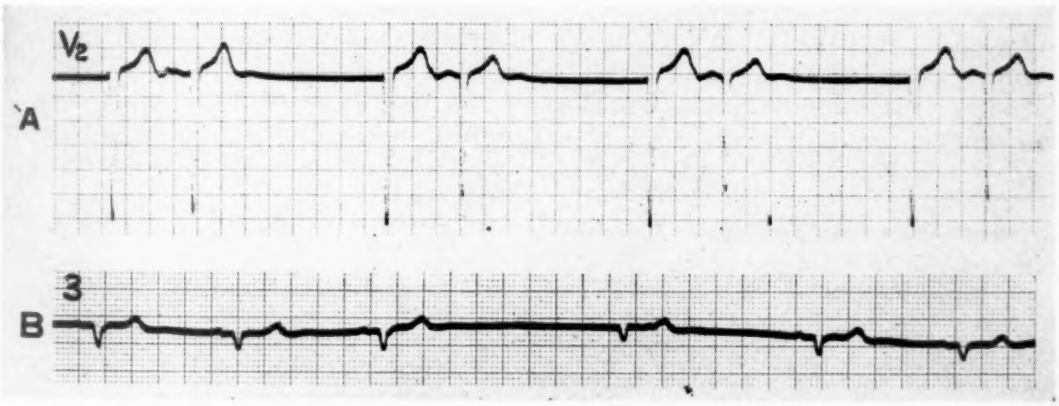

Fig. 2. (A). Bigeminal rhythm: of each couplet the first beat is a nodal escape beat and the second a conducted sinus beat. The first P wave is plainly visible; the last three barely deform the descending limbs of the T waves. Atrial rate, 27; nodal escape rate, 37. (B). Normal sinus rhythm interrupted by one sinus pause due to 2:1 S-A block. This pause is terminated by a nodal escape beat whose S-T segment is deformed by the next rhythmic P wave. Consecutive P-P intervals measure 106, 110, 216, 113, and 108 hundredths of a second.

Discussion

In 1946 Parsonnet and associates[1] reviewed and classified electrocardiographic bigeminy, listing no less than 27 mechanisms. Under the subheading of A-V nodal bigeminy they properly included pseudoreciprocal rhythm, which is an accepted term for the type of paired sequences here illustrated. But terms compounded with the prefix "pseudo-" are seldom satisfactory descriptively because they tell us only what the thing is *not;* they name the imitated but give no clue to the nature of the imitator. Despite this negative failing, such terms may be acceptable when there is only one possible masquerader; they are undesirable when there is more than one.

Reciprocal rhythm can be simulated by at least two mechanisms and of these only the poorer imitation enjoys the term "pseudoreciprocal." Pseudoreciprocal rhythm by definition is a phenomenon peculiar to A-V dissociation and consists of the pairing of a nodal (or ventricular) escape beat with a conducted atrial beat. This grouping thus resembles reciprocal rhythm in so far as it consists of a P wave sandwiched between two ventricular complexes; but the P wave in pseudoreciprocal rhythm is usually of normal sinus contour and this distinguishes it from the retrograde P wave of the true reciprocal beat. The second and better imitation consists of a nodal escape beat coupled with an ectopic atrial beat; here the aberrant P wave enhances the illusion of reciprocity.

We would therefore suggest that a simpler and more directly descriptive term, which leaves no doubt of the underlying mechanism, is *escape-capture sequence;* or, when the sequence is repeated to produce bigeminal rhythm, *escape-capture bigeminy.*

Relatively few examples of similar bigeminal rhythm have been reported.[2–21] In some of these the intervening P waves were aberrant.[8,12,13] Others, as Zeisler[7] first pointed out, were mistakenly reported as reciprocal rhythm.[16,17]

We can find but one example of escape-capture bigeminy set off by 2:1 S-A block. Padilla[5,6] twice published the same record in which a sudden halving of sinus rate led to nodal escape with resulting bigeminy for five couplets. The sinus rate then abruptly doubled to resume its previous rate with normal A-V conduction.

The tracings published by Zuidema[14] are of interest because they illustrate three different forms of bigeminy that can stem from A-V dissociation. One form is produced by the escape-capture sequence; a second by the coupling of ectopic atrial beats with nodal escape beats; and the third results from "concealed conduction"[22] occurring after every alternate ventricular beat.

The development of escape-capture bigeminy is presumably of no special significance in itself as it is dependent solely on an arithmetical caprice. In order for it to develop the rates of the dissociated atrial and ventricular pacemakers must be so adjusted that the escape interval is considerably shorter than the P-P interval—the escape beat must occur sufficiently soon after the capture beat so that the ensuing P wave will not fall due until the refractory period of the escape beat is over. This means that there must be a considerable disparity between the rates of the two pacemakers; thus in our case the atrial rate (27) was only 73 per cent of the ventricular rate (37). By contrast, in most cases of A-V dissociation the two competing rhythms have rates that are not greatly dissimilar.

Summary

(1) An example of A-V dissociation initiated by 2:1 S-A block with resulting bigeminal rhythm (pseudoreciprocal rhythm) is presented.

(2) Published examples of similar bigeminal rhythm are briefly reviewed.

(3) It is suggested that the terms "escape-capture sequence" and "escape-capture bigeminy" are descriptively preferable to pseudoreciprocal rhythm.

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Cardiac Amyloidosis

Electrocardiographic Findings

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THE OBJECT of this report is to direct attention to cardiac amyloidosis as a cause of heart failure and to describe the clinical and electrocardiographic findings in six cases representing this clinical entity.

While no definite diagnostic evidence can be obtained from the electrocardiogram, most tracings from patients suffering with cardiac amyloidosis are definitely abnormal and should suggest the diagnosis if the possibility of this disease is kept in mind.

Suspicion should be aroused if the extremity leads disclose QRS complexes of low amplitude, or if the auricular-ventricular conduction mechanism is impaired, or if the tracings show auricular fibrillation. In one of our cases electrical alternation of the P waves was an unusual finding, not previously reported. Complete or almost complete inversion of the QRS complexes in several of the precordial leads has been reported by other authors as a characteristic finding and this was also true in our cases. Such a pattern in the chest leads always raises the question of a healed or healing anteroseptal myocardial infarction. It is interesting in this connection that none of our patients complained of anginal pain before or during the time of observation. Lately we have done transaminase estimations and have found no significant elevations in cases of cardiac amyloidosis.

Heart failure was the most important diagnostic feature. Dyspnea and orthopnea were the chief complaints and represented the earliest symptoms. Ascites and peripheral edema were present in all cases. Chest x-ray revealed some cardiac hypertrophy and fluoroscopy diminished cardiac pulsation in some of our cases.

Microscopic examination revealed extensive involvement of the myocardium in all cases which came to autopsy. The myocardial blood vessels, the surrounding stroma and the subendocardial areas were particularly infiltrated with amyloid. In some regions large masses of amyloid completely replaced the muscle fibers.

It is customary to classify amyloidosis into primary, with etiology unknown, and secondary, following known chronic diseases. While the dominant feature in primary amyloidosis is involvement of the heart and in secondary amyloidosis involvement of liver, spleen, kidneys, skin, etc., such distinction is not always justified. In primary amyloidosis organs other

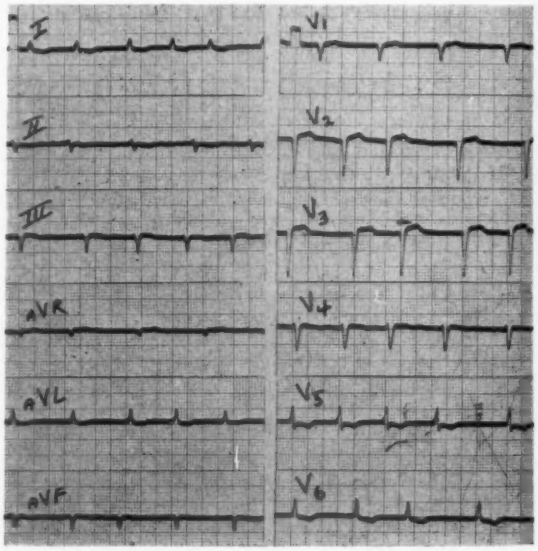

Fig. 1. Case 1. Low voltage in all extremity leads. Auricular fibrillation. Almost completely inverted QRS complexes in V_1, V_2, V_3 and V_4. (Note: All extremity leads of the electrocardiograms shown in this paper are recorded at 10 mm standardization and all precordial leads at 5 mm standardization).

than the heart may be affected and in secondary amyloidosis myocardial involvement does occur.

Case Histories

Case 1. A 60-year-old male complained of shortness of breath and swelling of both ankles of two months' duration. His appetite was poor and at times he was nauseated. On physical examination the cardiac rate was 120, the rhythm was regular. A few moist rales were heard at both bases. The liver was tender and extended three fingers' breadth below the right costal margin. There was pitting edema in both lower extremities. The blood pressure was 110/76. Laboratory studies including blood chemistry showed nothing unusual. The Congo red test was negative.

The electrocardiogram (Fig. 1) showed auricular fibrillation, low QRS voltage in the extremity leads, and changes in the precordial leads suggestive of scarring in the anterior wall of the left ventricle. This pattern, although not specific, should always suggest the possibility of cardiac amyloidosis.

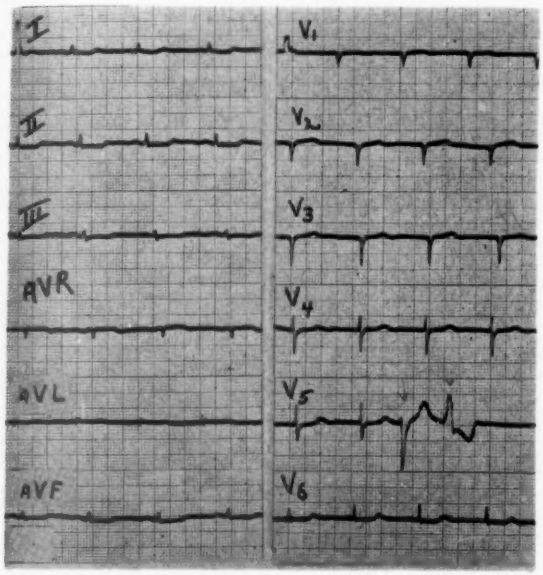

Fig. 2. Case 2. The extremity leads are of low voltage throughout. The precordial leads suggest scarring in the antero-septal region. Bidirectional ventricular premature contractions are seen in V_5. The ST segment depressions most likely are the result of digitalis.

Liver biopsy showed heavy masses of amyloid deposit. This patient improved under routine management for cardiac failure but finally became resistant to all treatment. He developed severe anasarca and pulmonary edema and died. Autopsy was refused.

Case 2. This 50-year-old white male was admitted to the hospital in severe cardiac decompensation. He was thin, dyspneic and appeared acutely ill. The pulse was feeble, regular at 60 per minute. Temperature was 101°, chest x-ray showed congestion of both lungs, the urine showed 3 plus albumin.

The electrocardiogram (Fig. 2) showed low QRS voltage in the extremity leads and QRS inversion in V_1, V_2 and V_3. The precordial leads suggest scarring in the anterior wall of the left ventricle.

This patient did not respond to routine treatment for congestive failure and died on the second day after admission. Autopsy showed amyloidosis of the heart, liver and kidneys.

Case 3. A 52-year-old woman entered the hospital in a state of unexplained, intractable heart failure with sudden onset. A liver biopsy ten days before death established the diagnosis of amyloidosis.

The electrocardiogram (Fig. 3) revealed extremely

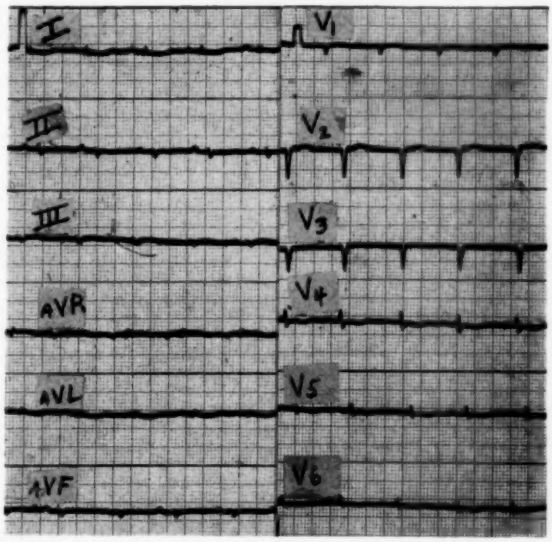

Fig. 3. Case 3. Very low voltage of all complexes in the extremity leads. Inversion of QRS complexes in V_1, V_2 and V_3. Electrical alternation of P waves, best seen in lead II (see also Fig. 4).

low voltage of the QRS complexes in the extremity loads. The R waves were almost absent in V_1, V_2 and V_3, suggestive of a healed anteroseptal myocardial infarction. These findings, in view of the liver biopsy, were best explained on the basis of cardiac amyloidosis.

Another interesting electrocardiographic finding in this case was the electric alternation of the P waves (Fig. 4). This I believe has not been previously reported in the literature in connection with cardiac amyloidosis.

This patient died rather suddenly one week after the above electrocardiogram was taken and autopsy showed extensive amyloidosis of the myocardium.

Case 4. A 60-year-old white male was admitted to the hospital complaining of abdominal swelling, dyspnoea, and ankle edema.

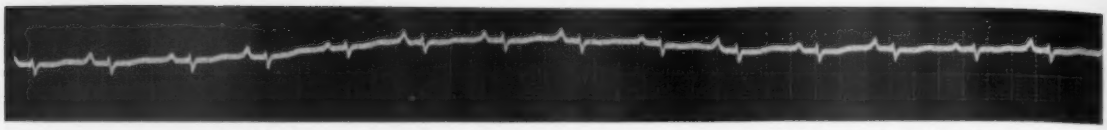

Fig. 4. Case 3. Lead II of the same tracing shown above in Figure 3 with higher standardization to demonstrate more clearly the electrical alternation of the P waves.

Physical examination revealed an acutely ill patient with moist rales in all lung fields, ascites and generalized edema. Blood pressure: 108/76. Laboratory examinations, including blood chemistry and liver function tests, were not striking except that the urine consistently contained 2 plus albumin. The electrocardiogram

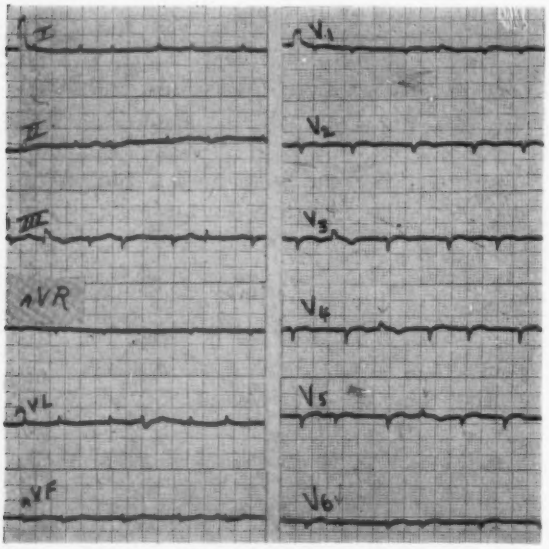

Fig. 5. Case 4. The extremity leads show low voltage throughout. There are frequent ventricular premature contractions and auricular fibrillation. The precordial leads suggest considerable scarring in the anterior wall of the left ventricle. No infarct, old or recent, was found at autopsy.

(Fig. 5) taken on admission showed auricular fibrillation, low amplitude of the QRS complexes in the extremity leads, loss of R waves in all precordial leads and ventricular premature contractions.

The patient's condition deteriorated rapidly in spite of treatment. He became comatose and died on the fifth hospital day. Autopsy showed primary amyloidosis of the heart, kidneys, spleen and liver.

Case 5. A 58-year-old male entered the hospital complaining of swelling of both legs and shortness of breath.

Physical examination showed a cardiac rate of 120 with irregular rhythm. The liver edge extended three fingers' breadths below the costal margin. There was pitting edema over both tibias. The lungs were clear. The important laboratory finding was a 4 plus albumin in the urine.

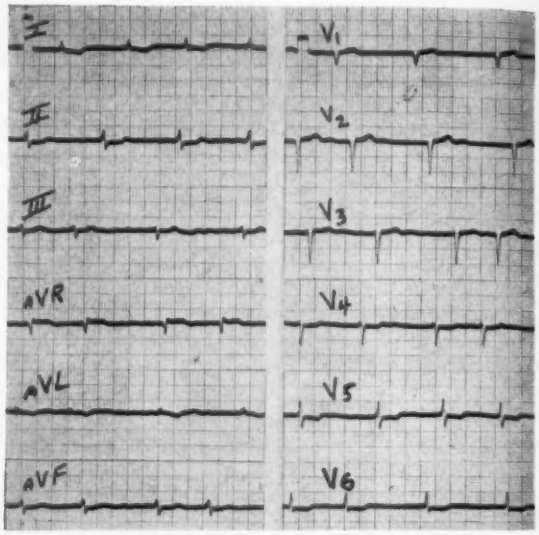

Fig. 6. Case 5. Auricular fibrillation with slow ventricular rate due to digitalis effect. Fairly low QRS voltage in the extremity leads. Inversion of QRS complexes in V_1, V_2, V_3 and V_4 (see also Fig. 7).

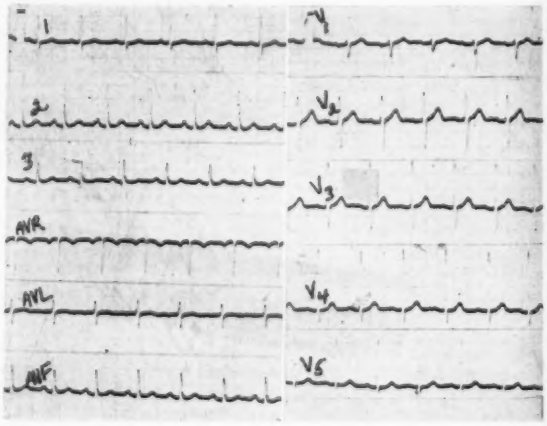

Fig. 7. Case 5: A routine electrocardiogram taken three years previous on the same patient whose tracing is shown in Fig. 6. He was in good health at that time, and the electrocardiogram is essentially within normal limits. Notice particularly the normal QRS voltage in the extremity leads and normal configuration of the precordial leads as compared to the previous ECG (Fig. 6).

The electrocardiogram (Fig. 6) showed auricular fibrillation, low QRS voltage in the extremity leads and almost completely inverted QRS complexes in V_1, V_2,

V_3 and V_4. A routine electrocardiogram (Fig. 7) was taken on this patient previously. It was essentially within normal limits. It is interesting to notice the changes which have occurred after the patient developed cardiac amyloidosis.

Congo red test was negative. There was marked macroglossia. The skin surrounding the mouth and nose showed translucent, waxy plaques which appeared solid on palpation. Skin biopsy showed extensive amyloid infiltration. This patient, although still alive, is in intractable heart failure at the time of this report.

Case 6. A 48-year-old white male complained of soreness and aching of the muscles and joints for 18 months. He suffered from intermittent febrile episodes with occasional purpuric spots in the lower extremities. Repeated studies and laboratory tests failed to reveal a definite diagnosis.

On his last hospital admission there was marked macroglossia, a dermatitis-like eruption on the face and hepatomegaly. Signs of congestive failure appeared soon after admission.

The outstanding findings in the electrocardiogram (Fig. 8) were auricular fibrillation, low QRS voltage in the extremity leads and inversion of the QRS complexes in the first three precordial leads.

Skin and liver biopsy showed the presence of amyloid. This man is at this time in intractable heart failure.

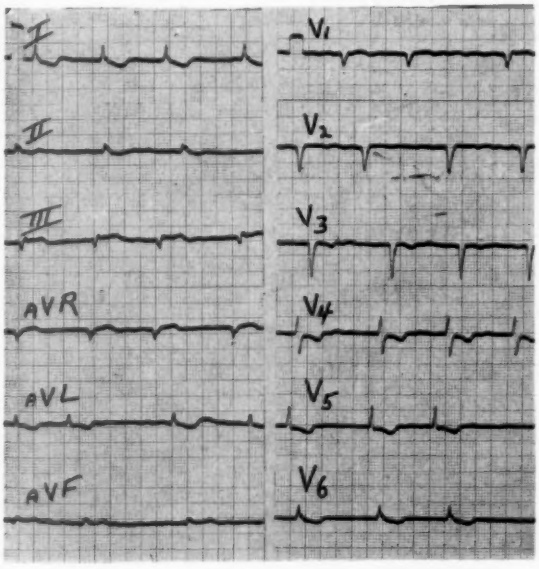

Fig. 8. Case 6. The electrocardiogram shows auricular fibrillation. Low QRS voltage in the extremity leads. Inversion of the QRS complexes in V_1, V_2 and V_3. Questionable pattern of posterior myocardial infarction. No history of chest pain.

Comment

Most of our patients presented the picture of progressive congestive heart failure. The usual treatment was only partially and temporarily effective. No definite cause for heart failure could be determined until the diagnosis of cardiac amyloidosis was established.

The electrocardiogram, while not specific, gave a suggestive pattern in all cases and was quite helpful in leading to the final, correct diagnosis. In the presence of low QRS voltage in the extremity leads, complete or almost complete inversion of the QRS complexes in the first three or four precordial leads, one should consider the possibility of cardiac amyloidosis. This pattern gains in importance if rhythmic disturbances, such as atrial fibrillation and conduction disturbances, are present. Electrical alternation of the P waves was an interesting and unusual finding in one of our cases.

Summary

Six cases of amyloidosis are reported. In the presence of intractable heart failure of undetermined origin cardiac amyloidosis should be suspected. The electrocardiographic findings suggestive of this entity are described.

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Sarcoidosis of the Heart*

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FROM THE individual concepts of localized disease involving variously the eyes and parotid gland, the lungs and the skin, there has evolved the panorama of an entity attacking almost all organs of the body. Described by Besnier in 1889 as lupus pernio, in 1899 by Boeck as sarcoid and united as Besnier-Boeck-Schaumann disease by the description of Schaumann in 1917, then amended to include Heerfordt's uveoparotid fever by Longcope and others in 1936,[28] the present view of sarcoidosis has appeared. Pathologic evidence of involvement of the heart in 28 cases was found in 23 reports reviewed by Peacock, Lippschutz and Lucas.[24] They added a 29th instance. We have found three others[25–27] and herewith present a 33rd case (Table I).

TABLE I

33 Cases of Myocardial Sarcoidosis[24]

Case Number	Age	Race	Sex	Reference Number
1	52	W	M	1
2	45	W	M	2
3	58	N	F	3
4	51	—	M	4
5	18	N	M	5
6	42	N	M	6
7	40	N	M	7
8	24	N	M	8
9	27	N	F	9
10	26	N	M	10
11	32	N	M	11
12	28	W	M	12
13	25	N	M	12
14	60	W	F	13
15	29	W	M	13
16	26	N	F	14
17	51	W	M	15
18	28	N	M	16
19	50	—	F	17
20	28	N	F	18
21	45	W	M	19
22	43	—	F	20
23	20	N	M	21
24	46	N	M	22
25	27	N	F	22
26	22	N	F	22
27	45	N	F	22
28	54	W	F	23
29	27	W	F	24
30	47	W	M	25
31	48	W	M	26
32	33	—	M	27
33	53	N	F	Present report

CASE HISTORY

M. T., a 53-year-old Negro woman, was first admitted to Albert Einstein Medical Center—Southern Division at the age of 43 on August 12, 1941. The only positive finding was a large nodular uterus. On the day after admission, a bilateral salpingo-oöphorectomy, hysterectomy and appendectomy were performed. The pathologic report was multiple fibromyomata, chronic salpingitis, hemorrhagic corpus luteum, corpus luteum cyst and a normal appendix. She was discharged on August 26, 1941.

Her next admission and the first pertinent to the present illness was on September 20, 1949, with a complaint that shortness of breath and a choking sensation in the throat had been present for nine months. She had had a low grade chronic cough since the onset of a "cold" in January, 1949. There was a ten pound weight loss in nine months. There was no history of tuberculosis. The blood pressure was 130/80. A nodule was palpated in the left lobe of the thyroid. A few rales were present at the left lung base. Liver and spleen were enlarged to palpation.

The following laboratory determinations were obtained: Urine was essentially normal. Complete blood count showed a hemoglobin of 69 per cent with 3.6 million red cells, 3,900 white cells of which 72 per cent were polys and 4 per cent were eosinophiles. Blood sugar was 84 and blood urea nitrogen was 8 mg/100 cc. Prothrombin time was 60 per cent, thymol turbidity 10.5 units and bromosulphalein showed 5 per cent re-

* From Medical Service #1, Albert Einstein Medical Center, Southern Division, Philadelphia.

tention in 45 minutes. Alkaline phosphatase was 5.1 Kay-Roberts units, total protein 8.5 g with 5 g of albumin and 3.5 g of globulin. Icterus Index was 6.4 units. Examination of sputum was negative for acid-fast organisms as was a gastric lavage. Sedimentation rate was 5 and 7 mm in five minutes.

Chest x-rays revealed enlargement of the right paratracheal and hilar lymph nodes and patchy infiltration of the lower lobes. Long bones and bones of the hand were normal to roentgen study. Barium enema revealed a malrotation of the cecum and ascending colon, which were present in the left lower quadrant. Intravenous urogram was essentially normal. The electrocardiogram showed slight sinus arrhythmia and bradycardia. A hematologic consultation found essentially normal values for the blood and bone marrow except for the presence of many target cells. The tuberculin test was negative. An eye consultation revealed a granulomatous anterior uveitis, compatible with the diagnosis of sarcoid. The thyroid nodule was excised on September 27. Microscopic examination revealed sarcoidosis. The patient was discharged on October 8, 1949.

Final admission was to the service of Dr. Theodore H. Mendell on July 6, 1950 because of chronic productive cough, marked dyspnea and weakness. There was no hemoptysis or pain. The appetite was poor and there was a weight loss of 30 lb since her previous admission. Examination revealed an emaciated dyspneic woman. There was dullness to percussion at both lung bases with crackling rales heard at all areas. The liver was palpated 6 fingers' breadth below the costal cage and was tender. The spleen was also palpably enlarged. The patient expired approximately 20 hours after admission.

Autopsy was performed by Dr. Alfred S. Conston three hours after death.

Summary of Autopsy Findings

GROSS PATHOLOGIC DIAGNOSIS

External Examination: Emaciation; petechiae; cervical scar (old thyroid biopsy); abdominal scar (old hysterectomy, appendectomy).

Internal Examination: Marked mediastinal adenopathy (sarcoid); perithyroid adhesions, old peritoneal petechiae (anoxic); peritoneal adhesions.

Blood Vessels: Aorta: Normal.

Heart: Moderate dilatation; epicardial petechiae (anoxic); endocardial hemorrhage, right ventricle; anomalous aortic valve cusp.

Lungs: Marked diffuse military parenchymal infiltrations (sarcoid); hilar adenopathy (sarcoid); anomalous lobation.

Spleen: Capsular adhesions; slight splenomegaly; sarcoid?

G. I. Tract: Acute hemorrhagic gastritis; old appendectomy; malrotation.

Liver: Slight hepatomegaly; pallor.

Gall Bladder: Low grade cholelithiasis.

Pancreas: Normal.

Adrenals: Moderate cortical atrophy; sarcoid?

Kidneys: Normal.

G. U. Tract: Old hysterectomy and salpingo-oöphorectomy; distension of bladder.

Lymph Nodes: Sarcoid.

Bone Marrow: Normal.

Brain: Not examined.

HISTOLOGIC DIAGNOSIS

Thyroid: Moderate atrophy; focal disseminated fibrosis; miliary sarcoid.

Blood Vessels: Slight atherosclerosis.

Heart: Marked chronic myocarditis; miliary sarcoid; focal myocardial hemorrhage (right ventricle).

Lungs: Extensive miliary (and confluent miliary) sarcoid; focal fibrosis; focal emphysema; congestion; focal hemorrhage.

Spleen: Congestion; slight miliary sarcoid; focal confluent miliary sarcoid.

G. I. Tract: Mucosal autolysis; congestion.

Liver: Moderate miliary sarcoid; low grade focal chronic hepatitis; slight edema.

Pancreas: Moderate congestion.

Adrenals: Cortical atrophy; lipoid depletion; focal slight necrosis.

Kidneys: Congestion; slight miliary sarcoid; slight focal chronic pyelonephritis; slight focal arteriolar nephrosclerosis.

Lymph Nodes: Marked confluent miliary sarcoid; marked focal fibrosis.

Bone Marrow: Moderate focal hyperplasia.

Microscopic Comment: Sections of the internal organs reveal diffuse involvement typical of sarcoid. The nodules are of the miliary type, although frequently confluent. Several varieties are seen; some are composed entirely of epitheliod cells; many contain one or more large giant cells; a few are necrotic; and some are fibrotic. The major involvement is in the lungs and lymph nodes. In the lung there is extreme parenchymal replacement so that, in many areas, little or no aerating tissue is present. In these areas there are occasional cystic bronchioles and alveoli, evidently a compensatory mechanism. Scattered throughout the

pulmonary and node lesions are innumerable laminated basophilic bodies, the Schaumann bodies, seen both within the gaint cells and lying free. No "asteroid" inclusions are seen. The lesions of sarcoid were noted (in decreasing order of involvement) in the following organs: lungs, lymph nodes, liver, heart, spleen, thyroid, kidney. In the viscera studied, only the following organs were free of sarcoid involvement: stomach, pancreas, adrenal, aorta. In addition to the described lesions, the heart also showed a diffusion chronic myocarditis.

Pathologic Diagnosis: (1) Generalized sarcoidosis, primarily involving lungs and mediastinal lymph nodes; (2) chronic myocarditis; (3) multiple serous membrane petechiae (anoxic type); (4) emaciation.

Comment: The cause of death in this emaciated 53-year-old Negro woman must be attributed to cardiorespiratory failure secondary to generalized sarcoidosis.

Comment

The diagnosis of sarcoidosis is becoming comparatively more frequent. This is due to an increased awareness of the disease incidence at various ages in both white and Negro population, male and female.

Recognition of the affliction has been enhanced by improved medical care throughout all strata of population, increased diagnostic facilities, particularly mass photofluorography of chests, more extensive study of the differentiation from tuberculosis, and the availability of pre-scalene node biopsy. Many cases are still being missed because of their mild or asymptomatic nature. In an unknown incidence in the general population, postmortem findings do not reflect accurately the intrinsic mortality rate of the disease nor do they suggest adequately involvement of the heart. Since Bernstein *et al.*[1] reported sarcoid lesions of the epicardium in 1929, 32 other proven instances have been noted (Table I). The autopsy incidence of myocardial sarcoidosis has been thought of as 20 per cent since Longcope and Freiman[29] made their report in 1952.

Although the diagnosis of cardiac involvement has been indicated only too infrequently during life, it can be made. Reports appearing increasingly in the literature point the way. First should be a high index of suspicion. Then there should be an awareness of suggestive electrocardiographic findings ranging from no recognizable abnormalities to RS-T segment and T wave changes[11] to any type of arrhythmia including frequent complete heart block. Of course, clinical evidence of cardiac incapacity culminating in heart failure or even sudden death adds fuel to the fire. Peacock *et al.*[24] reported sudden death in 10 cases of the 29 they reviewed. Three of the four instances added in this paper terminated in sudden or unexpected death, one during mitral valvulotomy.

Again, autopsy statistics do not reflect accurately the mild and transient involvement of the heart in the many reported and unreported cases. Also, we would like to point out that more than half of the cases in Table I (17 out of 33) were 40 years of age or over at death.

Summary

(1) The diagnosis of generalized sarcoidosis is being made more frequently.

(2) Four cases of myocardial involvement with death are added to 29 previously assembled, including one case report.

(3) A high index of suspicion will provide the diagnosis of myocardial involvement during life.

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Mediastinal Lymphoma Simulating Primary Heart Disease*

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INFILTRATION of the heart by lymphoma is rarely recognized clinically, despite the known tendency of this disease to involve many organs. In a clinical review of 732 cases of lymphoma with intrathoracic manifestations, Vieta and Craver[1] did not mention cardiac involvement. In a similar study of 55 cases of Hodgkin's disease, Walpaw and his associates[2] found invasion of the heart to be rare.

The diagnosis of cardiac involvement is usually made when signs of heart disease appear in a patient with known lymphoma. Because effective palliative therapy is available for the lymphoma, early and accurate diagnosis is of practical importance. We have recently seen two patients in whom the presenting clinical picture was that of heart disease. A diagnosis of mediastinal lymphosarcoma with cardiac involvement was made in both cases prior to death.

CASE HISTORIES

CASE 1. A 39-year-old man had a prolonged episode of polyarthritis involving his hips, knees and feet at age 10 for which he was kept at bed rest for several weeks. He made a complete recovery and was symptom-free until five months prior to hospitalization when he had vague discomfort in the substernal and right pectoral region, which persisted for three months. He was then hospitalized for one month with a diagnosis of active rheumatic pancarditis. There was a slight temperature elevation. The heart was markedly enlarged, and a harsh apical systolic murmur, a rumbling presystolic murmur, and a pericardial friction rub were heard. Transient episodes of atrial fibrillation occurred. An electrocardiogram revealed non-specific changes suggestive of myocarditis or pericarditis. An x-ray of the chest showed cardiac enlargement with straightening of the left border (Fig. 1). The lung fields were clear. Steroid therapy was administered with marked subjective improvement, subsidence of the fever, and decrease in the elevated sedimentation rate. Following his discharge from the hospital, steroid therapy was discontinued because of the onset of epigastric pain suggestive of peptic ulcer. There was prompt recurrence of the patient's previous symptoms of fever, chest pain, dyspnea and ankle edema. He was then hospitalized at the Philadelphia Veterans Administration Hospital.

On admission, May 14, 1954, he was acutely ill with a temperature of 101 degrees F and a pulse rate of 120/minute. The heart was markedly enlarged. There was a loud harsh systolic murmur at the apex and a rumbling crescendo presystolic murmur heard with maximum intensity in the 3rd interspace to the left of the sternum. There was a protodiastolic gallop at the

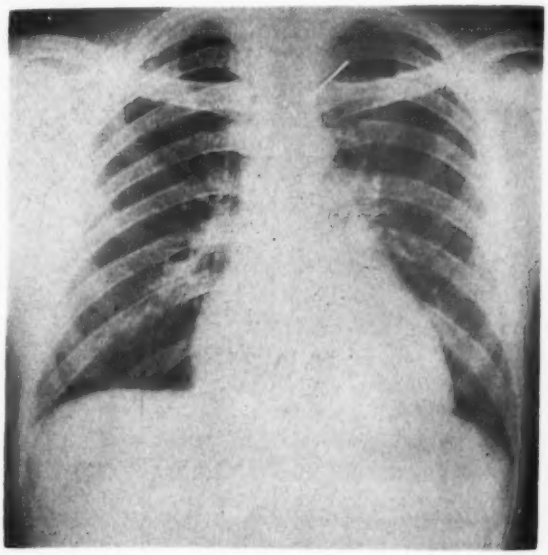


Fig. 1. Case 1. P-A roentgenogram of chest on 3-15-54 showing enlarged cardiac silhouette with straightening of the left cardiac border. Lung fields are clear.

* From the Medical Service and Cardiovascular Section, Veterans Administration Hospital, Philadelphia, Pennsylvania.

apex. The liver was felt 2 fingers' breadth below the right costal margin. A diagnosis of active rheumatic pancarditis with congestive heart failure was made but the possibility of subacute bacterial endocarditis was considered. He was thought to have a steroid induced peptic ulcer.

Routine laboratory studies were normal and several blood cultures were negative. Antistreptolysin and antihyaluronidase titers were in the normal range. An electrocardiogram revealed atrial fibrillation, right axis deviation and nonspecific ST segment and T wave changes. Serial electrocardiograms were unchanged except for alternation in the mechanism between atrial fibrillation and normal sinus rhythm.

Radiographic and fluoroscopic examination of the chest revealed marked cardiac enlargement and diminished cardiac pulsation. There were bilateral pleural effusions and nodular densities in both lower lung fields (Fig. 2). These densities were suggestive of metastatic disease, but the possibility of localized areas of fluid accumulation secondary to congestive heart failure was considered. Review of a chest film taken one month before admission revealed a large density in the right mid lung field (Fig. 3). Examination of the pleural fluid for malignant cells was negative.

The patient's course was one of rapid deterioration, with persistent low grade fever, severe dyspnea and episodes of disorientation. Repeated thoracenteses, antibiotics, digitalis and mercurial diuretics were ineffectual. A needle biopsy of one of the pulmonary masses revealed lymphosarcoma. The patient expired on the 21st day of hospitalization before definitive therapy could be initiated.

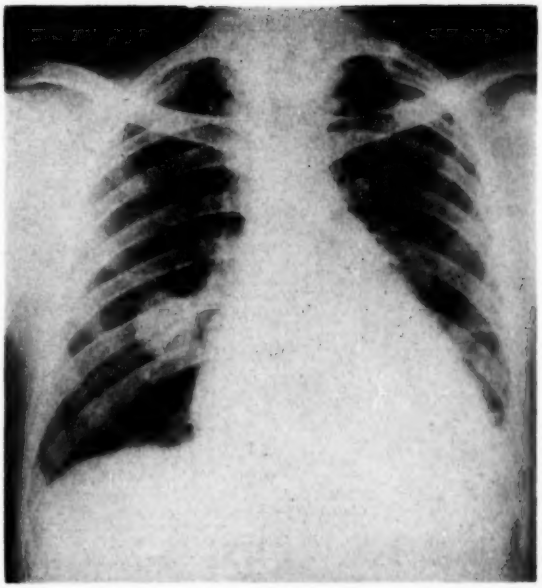
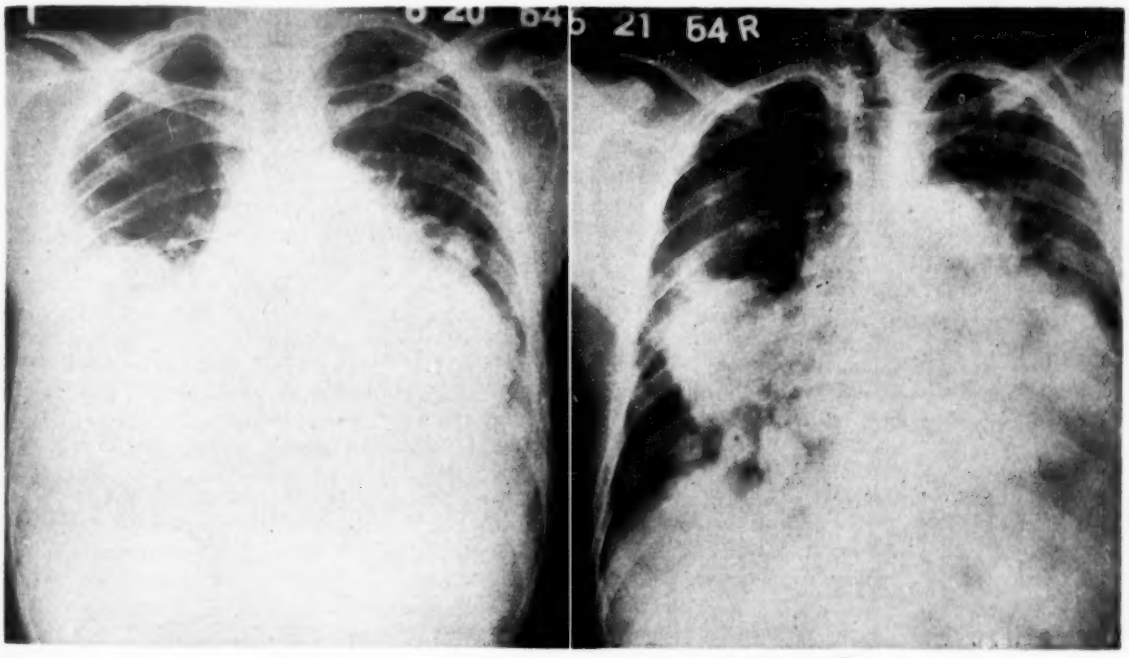
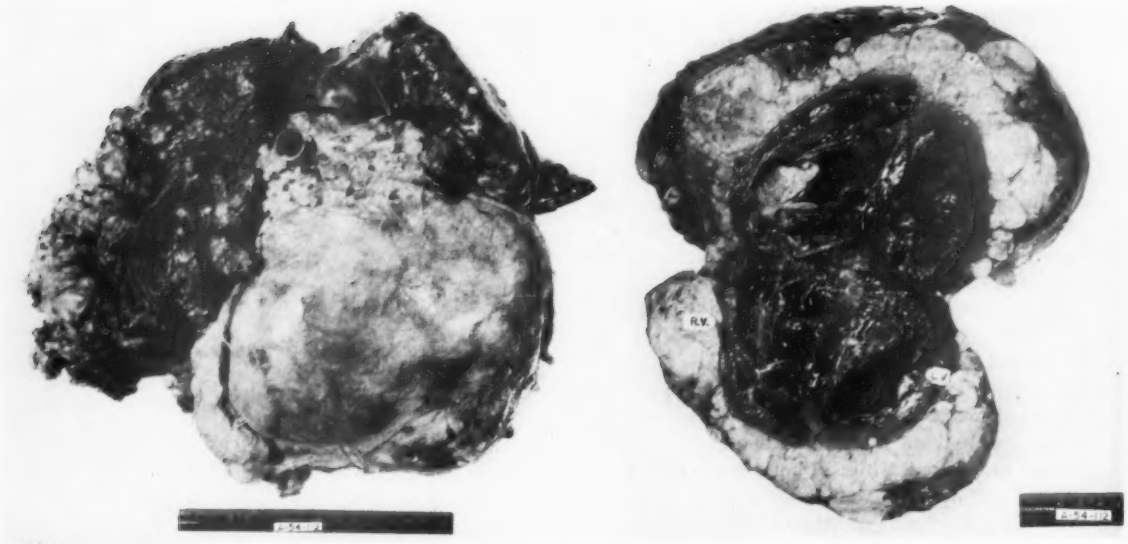


Fig. 3. Case 1. P-A roentgenogram of chest on 4-12-54 (one month before admission) showing large cardiac silhouette, small pleural effusions bilaterally, and a large density in the right midlung field. Other smaller nodules are faintly visible.



A B

Fig. 2. Case 1. (A) P-A roentgenogram of chest on 5-20-54 showing massive enlargement of the cardiac silhouette consistent with pericardial effusion, bilateral pleural effusion, and nodular densities throughout both lower lung fields partially obscured by pleural fluid. (B) Roentgenogram after thoracentesis showing clearly the nodular densities in both lungs.



A B

Fig. 4. Case 1. (A) Autopsy specimen showing tumor mass encasing the heart and great vessels. Numerous tumor nodules visible in lungs. (B) Horizontal section demonstrating tumor tissue surrounding and invading heart.

Postmortem Findings: At autopsy there was extensive involvement by a mediastinal tumor of all intrathoracic structures including the heart, great vessels and lungs. The heart was encased in a tumor mass which also enveloped the ascending aorta, aortic arch and pulmonary artery (Fig. 4). The endocardium in the region of the pulmonary valve showed several polypoid masses. The heart and tumor together weighed 2400 grams. Both lungs contained metastatic nodules. No tumor was found outside the thorax. Two partially healed ulcers were found in the duodenal bulb.

Microscopic examination confirmed the previous diagnosis of lymphosarcoma. There was invasion of the pericardium, epicardium, and the more superficial aspects of the myocardium, the great vessel walls, and the cusps of the pulmonary valve.

Case 2. A 33-year-old man was admitted to the Philadelphia Veterans Administration Hospital with a two-year history of nonproductive cough and a six-month history of weight loss, increasing exertional dyspnea, orthopnea and ankle swelling.

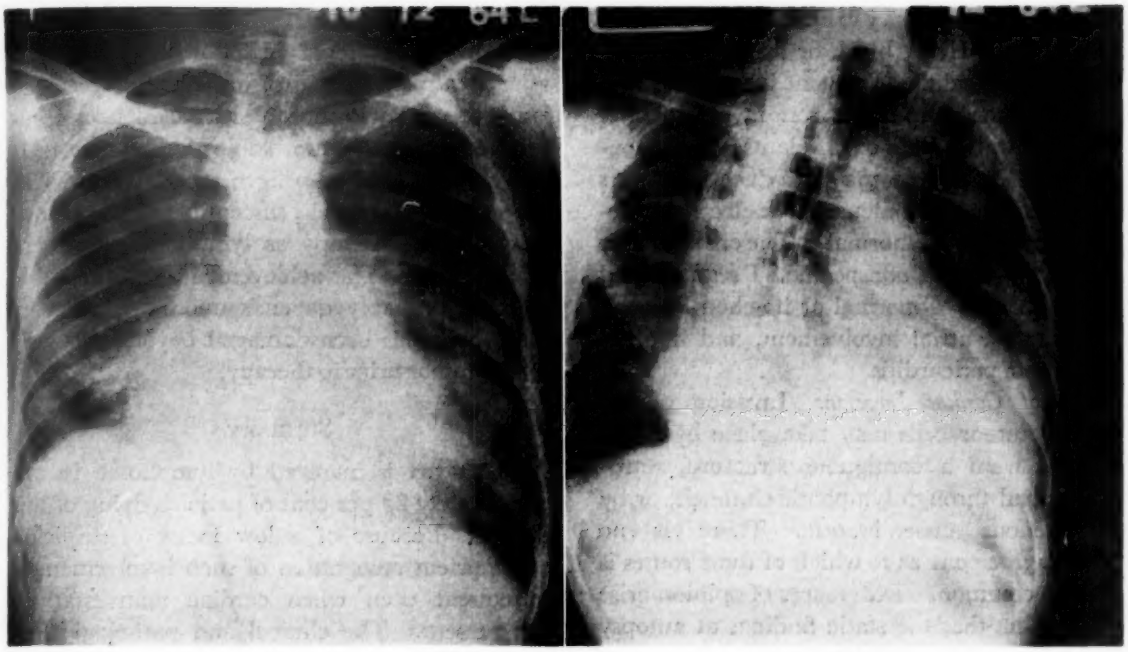
He was cyanotic and looked chronically ill. There was marked cardiac enlargement, a rapid heart rate and a late diastolic gallop. No murmurs were heard. Moderate pretibial pitting edema was present.

Urinalysis, blood chemistry determinations and liver function tests were within normal limits. There was a hypochromic microcytic anemia with a hemoglobin of 10 g/100 cc. Repeated blood, sputum and urine cultures were negative. Antistreptolysin and antihyaluronidase titers were normal. An electrocardiogram showed a right ventricular hypertrophy pattern. There were recurrent episodes of atrial fibrillation and flutter, requiring large doses of digitalis to control the arrhythmias. A phonocardiogram confirmed the presence of a presystolic gallop but revealed no other adventitious sounds. Bronchoscopy was negative.

Chest roentgenograms and fluoroscopy revealed marked cardiac enlargement and pulmonary vascular congestion. In the region of the left atrium extending posteriorly and to the right there was an unusual bulge which could not be separated from the heart shadow (Fig. 5). This was thought to be a large left atrium. An angiocardiogram demonstrated prominence of the pulmonary segment and a pericardial effusion, but did not confirm the original impression that the mass was a cardiac chamber. The possibility of tumor was considered, and exploratory thoracotomy was performed. A large mass was found in the posterior mediastinum, invading the right lower lobe and pericardium and encasing the heart. Resection was considered impossible and a biopsy was done. The histologic diagnosis was reticulum cell sarcoma. A course of x-ray therapy consisting of a tumor dose of 2600 R was administered in 21 days with some subjective improvement but no change in the size of the tumor.

Three months after completion of the irradiation the patient was readmitted to the hospital because of the recurrence of cough, dyspnea and cyanosis. His condition deteriorated rapidly and he expired on the fourth day of hospitalization.

Postmortem Findings: At autopsy a posterior mediastinal mass invading the heart was found. Tumor surrounded the superior and inferior venae cavae and pulmonary veins but did not encroach on their lumina. At the base of the interatrial septum there was a tumor nodule protruding into the right and left atria. Another nodule



A B

Fig. 5. Case 2. (A) P-A roentgenogram of chest showing marked cardiac enlargement and pulmonary congestion. Bulge on right border cannot clearly be differentiated from heart shadow. (B) Right oblique projection showing large globular mass projecting posteriorly in the region of the atria but not deviating the barium-filled esophagus.

was present on the anterior surface of the left ventricle. The pericardial cavity contained 200 cc of bloody fluid. No evidence of primary heart disease was found. There was a large tumor mass at the bifurcation of the trachea and there were two small nodules on the pleura, but no tumor was found outside the thorax.

Microscopic examination revealed undifferentiated lymphoma invading all layers of the heart with large areas of necrosis thought to be secondary to irradiation.

Discussion

Involvement of the heart by metastatic malignancy, once considered rare, is now recognized with increasing frequency by the pathologist. Cardiac metastases are found at autopsy in 5 to 20 per cent of all patients dying of neoplastic disease.[3–12] The heart is involved in approximately 20 per cent of lymphoma, bronchogenic carcinoma and carcinoma of the breast. This incidence is consistently exceeded only by that in malignant melanoma and myelogenous leukemia in which it approaches 50 per cent.

Although cardiac involvement by tumor does not often dominate the clinical picture, cases of lymphoma whose presenting symptomatology suggested primary heart disease have been reported.[13–22]

The clinical picture of lymphomatous involvement of the heart is variable and is determined by the location and extent of the tumor. The frequency of antemortem diagnosis would be increased by a high index of suspicion and careful observation in patients with known lymphoma, particularly in those with mediastinal disease. In many of the patients found at autopsy to have cardiac involvement by tumor, no cardiac studies had been performed. In others abnormal cardiac findings had been attributed to different etiologic factors, despite the known diagnosis of lymphoma or the presence of mediastinal lymphadenopathy.

Signs of Cardiac Involvement: Neoplastic involvement of the heart is most often manifested by signs due to invasion of the pericardium, such as pericardial friction rub or pericardial effusion, usually bloody. Cardiac tamponade may be produced either by the effusion or by encasement of the heart in tumor tissue. A somewhat less frequent manifestation is heart failure and

gallop rhythm secondary to extensive myocardial involvement. Heart block or arrhythmia may occur if the conduction system is invaded, and arrhythmia may also result from involvement of the atrial wall. Tumor implants on the endocardium or valves may produce murmurs and obstructive phenomena. The electrocardiogram is frequently abnormal. The changes may include low voltage, nonspecific ST segment and T wave changes, abnormal or notched P waves which suggest atrial involvement, and findings suggestive of pericarditis.

Mode of Cardiac Invasion: Invasion of the heart by tumor cells may take place by direct extension from a contiguous structure, retrograde spread through lymphatic channels, or by hematogenous dissemination. There is no general agreement as to which of these routes is the most common. Differences of opinion arise from the fact that the static findings at autopsy are difficult to interpret in terms of dynamic processes during life. In all likelihood the route of invasion varies according to the type of tumor. Leukemia and melanoma which often arise at a distance are most likely disseminated via the blood stream, whereas such tumors as lymphoma, bronchogenic carcinoma and breast carcinoma probably utilize the other two avenues of spread. Although earlier studies suggested that right atrial involvement was most common, the consensus at present is that all four chambers are involved with a frequency proportionate to their mass.[7,10]

Treatment: Little is known about the therapy of lymphomatous involvement of the heart and results are difficult to evaluate because of the paucity of cases reported. Nabarro[16] described a 32-year-old man with atrial flutter, congestive heart failure, and cyanosis who did not respond to either conventional cardiac therapy or antilymphomatous therapy. Garvin[23] reported a good response to x-ray therapy in a 27-year-old woman with atrial fibrillation and congestive heart failure due to Hodgkin's disease. A remission of several months' duration was achieved. Hagans[18] reported a complete remission in a patient with Hodgkin's disease and massive pericardial effusion after a course of x-ray therapy to the mediastinum and nitrogen mustard. The heart returned to normal size and the patient was symptom free at the time of the last reported follow-up six months after treatment. One of our patients received x-ray therapy with no objective evidence of improvement and little subjective change. It seems reasonable to believe that lymphoma in the heart should be as susceptible to the known modalities of therapy as lymphoma elsewhere in the body. The achievement of a favorable response probably depends upon whether cardiac tissue has been damaged beyond recovery by the tumor prior to therapy.

Summary

The heart is involved by lymphoma in approximately 20 per cent of patients dying of this disease. Because of a low index of suspicion antemortem recognition of such involvement is infrequent even when cardiac manifestations are present. The clinical and pathologic features of lymphomatous heart disease are briefly reviewed and two illustrative cases presented. Patients with known lymphoma should be carefully observed for signs of cardiac invasion and lymphoma should be considered in the differential diagnosis of heart disease of obscure etiology.

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Diagnostic Shelf

Atrial Septal Defect vs. Mitral Valve Disease

HISTORY

The patient,* a 43-year-old white woman, was admitted to the hospital with a history of pain in the chest and back, and right upper quadrant tenderness, for approximately six weeks. The patient stated that she had had a heart murmur as a child. She denied having had rheumatic fever but stated that she had had scarlet fever and diphtheria. The patient had had two uneventful pregnancies. For the previous few years, her only symptom had been dyspnea when climbing three flights of stairs. She had been placed on digitalis. The patient denied orthopnea, ankle edema, and nocturnal dyspnea. She had a slight cough with expectoration of white mucus, palpitation, and nocturia.

PHYSICAL EXAMINATION

Pulse 100, regular; blood pressure, 90/60. Well-nourished woman lying flat in bed in no acute distress. Bilateral distention of jugular veins. Chest resonant throughout with no rales. *Heart:* borders 5 x 13.5 cm; mitral configuration. Mid-diastolic thrill at apex, systolic thrill over the 2nd left interspace. Apical harsh systolic and mid-diastolic murmur; P_2 greater than A_2. *Abdomen:* The liver was palpable three fingers below the right costal margin and was tender. There was a questionable pulsation of the liver. No edema. No petechiae were noted.

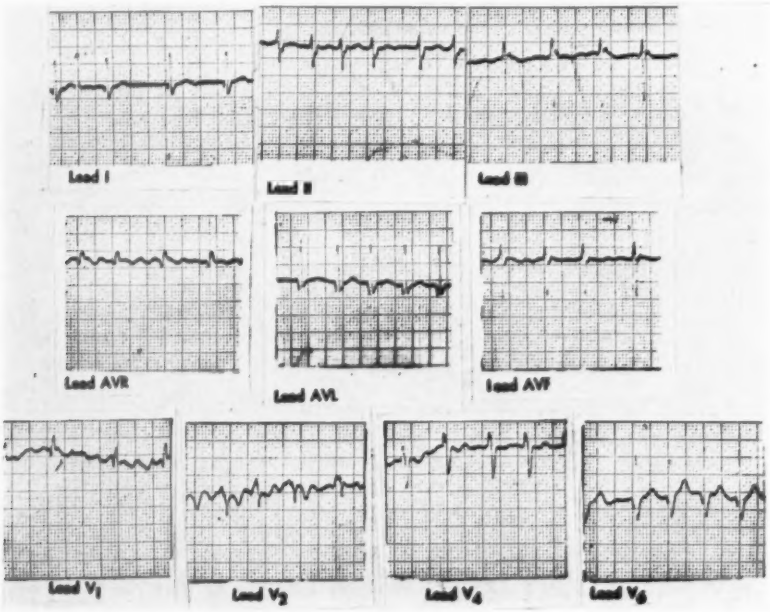

Fig. 1. Electrocardiogram taken during second admission.

CLINICAL DIAGNOSIS

The clinical diagnosis was: "rheumatic heart

* From Dr. E. B. Freilich's Service at Mount Sinai Hospital, Chicago.

disease with mitral stenosis and insufficiency, and probable aortic stenosis." In a second admission, which followed a profuse hemoptysis, a loud systolic murmur was heard over the pulmonic area.

LABORATORY DATA

The laboratory data were as follows:

Urine: Normal.

Blood: Normal Hb, RBC, WBC and differential. Chemistry—normal. Serology for syphilis—negative. Culture—negative.

Circulation Times: Arm to tongue = 30 seconds. Arm to lung = 22 seconds.

X-ray: Diffuse enlargement of the heart with prominent pulmonary "conus" and enlargement of both atria. Diagnosis: mitral plus tricuspid lesions.

GRAPHIC TRACINGS

Electrocardiogram: (1st admission) Sinus rhythm; no axis deviation; P-R = 0.24; double-peaked P waves in leads 2 and aVF; normal QRS; inverted T_3. A tracing recorded during the second admission revealed atrial fibrillation and incomplete right bundle branch block (Fig. 1).

Phonocardiogram: Presystolic gallop and systolic murmur at apex. No diastolic murmur, no delay of 1st sound, no opening snap. Presystolic murmur over 2nd right interspace. Systolic pulmonic murmur (Figs. 2A and B).

Jugular Tracing: Double-peaked A wave (Fig. 2B).

Hepatic Tracing: Large A wave in presystole. No evidence of tricuspid regurgitation (Fig. 2B).

Electrokymogram: Both the left and right atrial tracings reveal an unusual depth of atrial contraction (Fig. 2C).

DIAGNOSIS

The pattern of right bundle branch block; the presystolic gallop at apex coupled with a presystolic murmur over the tricuspid area; the large systolic pulmonic murmur; and the large presystolic wave in various tracings led to the revised diagnosis of either *atrial septal defect*, or *tricuspid stenosis with minimal mitral valve lesion.*

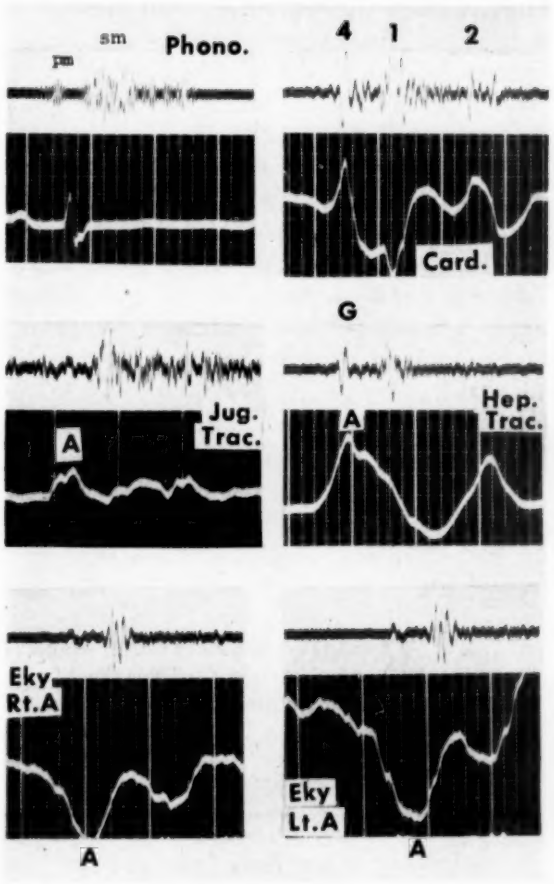

Fig. 2. (A). Phonocardiogram (upper tracings) recorded at pulmonic and mitral area. The lower tracings are the electrocardiogram and cardiac apex beat. (B). Jugular and hepatic pulse tracings showing tall double peaked A waves. (C). Electrokymograms of right and left atria showing deep A waves.

AUTOPSY

Autopsy disclosed a congenital malformation consisting of an atrial septal defect (foramen primum) plus a foramen ovale. The valves were normal.

DISCUSSION

In this case, several data indicated both right and left atrial hypertrophy: The electrocardiogram showed a curious type of double-peaked P wave in lead 2 with the second phase higher than the first; the electrokymograms of the atria revealed unusual depth of both the right and left presystolic waves; a presystolic gallop sound was recorded at the apex; and the hepatic tracing presented a tall A wave. These

data are different from those of cor pulmonale or tricuspid stenosis where the left atrial contraction is normal; they are different from those of mitral stenosis, where right atrial contraction is normal or moderately increased.

The murmurs recorded in this case were not consistent with those of rheumatic heart disease. No diastolic rumble was recorded at the apex and there was no opening snap. There was a moderate systolic murmur at the apex and a larger systolic pulmonic murmur indicating either increased pressure or increased flow in this vessel.

Right bundle branch block (incomplete) developed late in the course of the disease. This would be consistent with either mitral stenosis (disproven by the absence of the typical murmur) or tricuspid insufficiency (disproven by the lack of a plateau pattern in systole in the hepatic tracing and in the electrokymogram of the left atrium). Therefore, a septal defect, most likely an atrial septal defect, was the only acceptable diagnosis. A confirmation could be found in the presystolic murmur recorded at the 2nd left interspace (blood passing through atrial septum from left to right) and in the double-peaked A wave of the jugular tracing.

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Readers are invited to submit reports of interesting cases and illustrative tracings for this department. These should not exceed 1,000 words in length. Although not necessarily original, all material submitted should have teaching value.

Coming in the June Issue . . .

Use of Radioactive Iodine in the Treatment of Angina Pectoris . . . Oral Nicotinic Acid for Hyperlipemia . . . Aneurysms of the Thoracic Aorta . . . Comparison of Digitalis Glycosides

Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

Investigators and research workers are invited to submit, with a view to publication in an early issue, résumés of work in progress or recently completed.

A New Device for Recording Heart Sounds

CARDIOLOGISTS have long known that certain heart sounds and murmurs of low intensity may be audible on careful stethoscopic examination and yet will not be recorded on the phonocardiogram. For this reason, there has been a need for a practical electronic method of detecting and recording heart sounds and murmurs of very low intensity. However, in order to do this, it is necessary to have a pickup which has high sensitivity and wide range, and extremely low levels of ambient noise, both in the recording system and in the environment. Such a pickup has been devised by Dr. Dale Groom and associates at the Medical College of South Carolina, and in the General Motors Corporation. It is different from the ordinary type of pickup because it does not involve air conduction of sounds. It consists essentially of a capacitance transducer which can utilize the body surface itself as one electrode of the capacitor.

The pickup is a relatively simple device. It uses the principle of variation in electrical capacitance between two charged conductors, in accordance with change in the relative distance between these conductors. Therefore, one electrode of the capacitor is suspended above the skin while the body surface itself, or a suitable diaphragm serves as the other capacitor electrode (*Am. Heart J.* 54: 593, 1957). The chest wall vibrations which occur with the heart beat are converted by this capacitance device into electrical signals which are then amplified electronically and recorded.

Application of this relatively simple device in a soundproof room enables one to record or to amplify sounds which are at and below the threshold of stethoscopic audibility, including systolic murmurs present in a high percentage of fetal and presumably normal adult hearts. An interesting research application lies in its capability of recording sounds directly from the surface of the open heart without touching the surface.

The Pathology of Coronary Artery Disease: Indications for Surgery

IN ORDER to evaluate the applicability of direct technics, such as endarterectomy and coronary artery grafting, in the surgical treatment of coronary artery disease, an unselected group of 113 hearts obtained at autopsy was examined by Drs. Richard T. McDonald, D. Emerick Szilagyi, Lloyd C. France and Joseph C. Sieracki (Henry Ford Hospital, Detroit).

Pathological Findings: For the demonstration of the coronary artery system, a modified injection method of Meade and Bledsoe was used. Radiograms were made of the injected specimens in two planes after rotation of 180°. Angiographic and pathologic findings were carefully correlated.

Of the 113 specimens 39 were angiographically and grossly normal.

Seventy-four specimens demonstrated lesions of one or more coronary arteries. These specimens were divided into four groups:

(1) those with no subjective evidence of coronary disease, (2) those with clinical symptoms other than angina pectoris, and with positive electrocardiographic findings, (3) those with angina pectoris, and (4) those with clinical symptoms in association with diabetes mellitus.

The first group included nine females with an average age of 62 years and 22 males with an average age of 61.5 years. The lesions consisted of 15 single stenoses, 8 multiple stenoses, and 9 occlusions. In the second group there were 8 females and 14 males, both with an average age of 65 years. The lesions were those of 15 single stenoses, 16 multiple stenoses, and 16 occlusions. Twelve patients comprised the third group. Eleven were males with the average age of 69.9 years and one was a female aged 54 years. The lesions present were 6 single stenoses, 12 multiple stenoses, and 11 occlusions. There were 9 patients in the fourth group, four females with an average age of 60.2 years and 5 males with an average age of 65.0 years. One single stenosis, 10 multiple stenoses, and 14 occlusions were found.

Operability of Lesions: In order to be classified as operable, a lesion had to fulfill the following criteria:

(1) The lesions must have been within 5 cm of the orifice of the respective artery.

(2) The luminal diameter must have been no less than 2 mm.

(3) A satisfactory outflow must have been present.

The specimens were designated *inoperable* if no surgical attack seemed feasible by direct approach; *palliable*, if some improvement of the blood flow seemed possible through partial correction of the occlusion; and *curable*, if the complete correction of the occlusion appeared possible. So judged, in this series, 35.9 per cent of the specimens were inoperable; in 52.4 per cent of the cases palliation could probably have been achieved; and only 12.7 per cent of the cases had theoretically curable lesions.

Forty-three per cent of the specimens with significant pathology came from patients without clinical evidence of coronary atherosclerosis. Most of the curable lesions were in this group. In contrast, among the cases with clinical manifestations, only 10 per cent of the specimens revealed curable lesions. Angina was shown by this study to be the manifestation of advanced coronary disease: all the cases with this symptom had two or three arteries involved and none of the cases was curable. The instances of atherosclerosis in association with diabetes mellitus were the severest of all.

This study suggests that when coronary atherosclerosis is clinically manifest, it tends to be generalized and is rarely suited for cure by direct surgical procedures.

College News

Seventh Annual Meeting

GENERAL CONVENTION SCHEDULE

Chase-Park Plaza Hotel, St. Louis, Mo., May 20 to 24, 1958

May 19 through May 24—Press and Publicity—Pony Express Room—Chase—Lobby Floor
May 20 through May 24—Ladies' Hospitality Room—Georgian Room—Park Plaza
May 20 (Noon–5 P.M.)—Set up Exhibits—Exhibit Hall—Chase
May 20 (6 P.M.—Midnight)—82nd Board of Trustees—Lido Room—Chase—Lobby Floor

Wednesday, May 21

8 A.M.–6 P.M.—*Registration*—Exhibit Hall
9 A.M.–6 P.M.—Technical and Scientific Exhibits—Exhibit Hall—Chase
10 A.M.–Noon—1st Scientific Session—Khorassan Room—Chase—Lobby Floor
Noon–2 P.M.—Medical Motion Pictures—Regency Room—Chase—Lobby Floor
Noon–2 P.M.—Board of Governors' Luncheon Meeting—Colonial Room—Chase—2nd Floor
2–5:30 P.M.—2nd Scientific Session—Khorassan Room—Chase—Lobby Floor
6–6:45 P.M.—Reception—Tiara Lounge—Park Plaza—20th Floor
6:45–8 P.M.—Dinner—Tiara Room—Park Plaza—20th Floor
8–10 P.M.—Fireside Conferences—Tiara Room—Park Plaza—20th Floor

Thursday, May 22

9 A.M.–5 P.M.—*Registration*—Exhibit Hall
9 A.M.–5 P.M.—Technical and Scientific Exhibits—Exhibit Hall—Chase
9 A.M.–Noon—3rd Scientific Session—Khorassan Room—Chase—Lobby Floor
Noon–2 P.M.—Medical Motion Pictures—Regency Room—Chase—Lobby Floor
1:30–3:30 P.M.—4th Scientific Session—Khorassan Room—Chase—Lobby Floor
4–5:30 P.M.—7th Annual Business Meeting—Starlight Roof—Chase
6–6:45 P.M.—Cash Bar—Zodiac—Chase
6:45–8:15 P.M.—Buffet—Starlight Roof
8:30–10:30 P.M.—Convocation: Honorary Fellowships and Presentation of the Groedel Medal—Groedel Memorial Lecture—Khorassan Room—Chase—Lobby Floor

Friday, May 23

9 A.M.–5 P.M.—*Registration*—Exhibit Hall
9 A.M.–5 P.M.—Technical and Scientific Exhibits—Exhibit Hall—Chase
9 A.M.–Noon—5th Scientific Session—Khorassan Room—Chase—Lobby Floor
Noon–2 P.M.—Medical Motion Pictures—Regency Room—Chase—Lobby Floor
2–5:30 P.M.—6th Scientific Session—Khorassan Room—Chase—Lobby Floor
6:30–7:30 P.M.—Reception and Cocktails—Khorassan Room—Chase—Lobby Floor
7:30–9:30 P.M.—Seventh Annual Banquet—Khorassan Room—Chase—Lobby Floor
9:30–10:30 P.M.—Professional Entertainment—Khorassan Room—Chase
10:30–Midnight—Dancing—Khorassan Room—Chase—Lobby Floor

Saturday, May 24

9 A.M.–1 P.M.—*Registration*—Exhibit Hall—Chase
9 A.M.–1 P.M.—Technical and Scientific Exhibits—Exhibit Hall—Chase
9 A.M.–Noon—7th Scientific Session—Khorassan Room—Chase—Lobby Floor
Noon to 2 P.M.—Medical Motion Pictures—Regency Room—Chase—Lobby Floor
1:30–5 P.M.—8th Scientific Session—Khorassan Room—Chase—Lobby Floor
5 P.M.—Official Closing of the Convention
5–11 P.M.—83rd Board of Trustees Dinner Meeting—Lido Room—Chase—Lobby Floor

SCIENTIFIC PROGRAM

Chairman: JOHN S. LA DUE, M.D., F.A.C.C.

First Scientific Session

Wednesday, May 21, 1958, 10 A.M. to Noon

Symposium on
INFARCTION AND THROMBOEMBOLISM

Chairman: EDWARD MASSIE, M.D., F.A.C.C.
Director of Cardiovascular Clinic, Washington University and Director of Heart Station, Jewish Hospital, St. Louis, Mo.

1. Electron Microscopic Studies of Early Stages of Experimentally Produced Myocardial Infarction.
   RICHARD E. BRYANT, A.B. and ROBERT M. O'NEAL, M.D.
   Department of Pathology, Washington University School of Medicine, St. Louis, Mo.
   Discussion to be opened by JOHN R. SMITH, M.D.

2. Experiences with Fibrinolytic Therapy in Patients with Acute Myocardial Infarction.
   ANTHONY P. FLETCHER, M.D., NORMA ALKJAERSIG, M.S., FOTUS E. SMYRNIOTIS, M.D., and SOL SHERRY, M.D.
   Department of Medicine, Jewish Hospital, St. Louis, Mo.
   Discussion to be opened by JOHN S. LA DUE, M.D.

3. Mechanism of Pulmonary Infarction.
   JOHN R. SMITH, M.D.
   Department of Medicine, Washington University School of Medicine, St. Louis, Mo.
   Discussion to be opened by KENNETH C. PRICE, M.D.

4. Dietary Production of Myocardial Infarction.
   WILBUR A. THOMAS, M.D., W. STANLEY HARTROFT, M.D., and ROBERT M. O'NEAL, M.D.
   Department of Pathology, Washington University School of Medicine, St. Louis, Mo.
   Discussion to be opened by RICHARD J. BING, M.D.

Second Scientific Session

Wednesday, May 21, 1958, 2 to 5:30 P.M.

Symposium on
EFFECT OF STRESS AND ENVIRONMENT ON CARDIAC FUNCTION

Moderator: ERNST JOKL, M.D., F.A.C.C.
Professor of Physiology, Kentucky Rehabilitation Center, University of Kentucky, Lexington, Ky.

1. Physiology and Methods of Evaluation.
   ROBERT P. GRANT, M.D., F.A.C.C.
   National Heart Institute, Bethesda, Md.

2. Sudden Collapse and Death Following Physical Stress.
   ERNST JOKL, M.D., F.A.C.C.
   Professor of Physiology, Kentucky Rehabilitation Center, University of Kentucky, Lexington, Ky.

3. Environmental Aspects.
   CAPT. ASHTON E. GRAYBIEL, M.C., F.A.C.C.
   Naval Air Station, Pensacola, Fla.

4. Exercise in Patients with Heart Disease.
   SAMUEL FOX, III, M.D.
   National Heart Institute, Bethesda, Md.

5. Cardiac Stress as a Problem in Industrial Medicine.
   G. W. H. SCHEPERS, M.D., F.A.C.C.
   Institute of Industrial Health, University of Michigan Medical School, Ann Arbor, Mich.

6. Panel Discussion: To be opened by ALFRED D. DENNISON, M.D., F.A.C.C.

Fireside Conferences

Wednesday, May 21, 1958, 8 to 10 P.M.

1. Phonocardiography as an Office Procedure.
   ALDO LUISADA, M.D., F.A.C.C.
   Associate Professor of Medicine and Director, Division of Cardiology, Chicago Medical School and Mount Sinai Hospital, Chicago, Ill.

2. Surgical Treatment of Acquired Heart Disease.

DWIGHT E. HARKEN, M.D., F.A.C.C.
Associate Clinical Professor of Surgery, Harvard Medical School; Surgeon, Peter Bent Brigham Hospital, Boston, Mass.

3. Surgical Treatment of Acquired Heart Disease.
   CHARLES P. BAILEY, M.D., F.A.C.C.
   Professor of Surgery, Hahnemann Medical School, Philadelphia, Penna.

4. Pulmonary Embolism.
   D. W. CHAPMAN, M.D.
   Baylor University College of Medicine, Houston, Tex.

5. Sodium and Potassium Metabolism in Heart Disease.
   GEORGE B. MENEELY, M.D., F.A.C.C.
   Associate Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.

6. Traumatic Heart Disease.
   JAMES C. DRYE, M.D.
   Associate Professor of Surgery, University of Louisville, Louisville, Ky.

Third Scientific Session

PRESENTATION OF SCIENTIFIC PAPERS BY MEMBERS

Thursday, May 22, 1958, 9 A.M. to Noon

Chairman: ALDO A. LUISADA, M.D., F.A.C.C.
Division of Cardiology, Chicago Medical School and Mount Sinai Hospital, Chicago, Ill.

1. Comparison of Clinical and Hemodynamic Results of Mitral Commissurotomy One to Three Years After Surgery.
   PAUL KEZDI, M.D., F.A.C.C. and HANS WESSEL, M.D.
   The Cardiovascular Laboratory, Wesley Memorial Hospital and Department of Medicine, Northwestern University Medical School, Chicago, Ill.

2. Initial Ultra-Low Frequency BCG Complexes in Major Arterial Obstruction.
   JAN NYBOER, M.D., F.A.C.C. and ROONEY WILLARD, M.D.
   Department of Cardiovascular Physiology, Harper Hospital, Detroit, Mich.

3. External Phonocardiogram Compared with Intracardiac Phonocardiogram in Atrial Septal Defect.
   C. K. LIU, M.D., F.A.C.C. and A. JACONO, M.D.
   Division of Cardiology, Chicago Medical School and Mount Sinai Hospital, Chicago, Ill.

4. The Value of Newer Roentgenographic Dye Study Technics in the Analysis of Acquired Cardiovascular Disease.
   WILLIAM LIKOFF, M.D., F.A.C.C. and JOSEPH F. URICCHIO, M.D.
   Division of Medicine, Bailey Thoracic Clinic, Philadelphia, Penna.

5. The Alveolar Hypoventilation Syndrome; A Rare Cause of Heart Failure.
   RALPH E. SMITH, M.D., JAMES L. BROWN, M.D., and WAYNE HOSETH, M.D.
   Cardiovascular Disease Section, Veterans Administration Hospital, and Department of Medicine, University of Minnesota, Minneapolis, Minn.

6. The Successful Use of Induced Hypometabolism for the Elimination of Arrhythmias in the Euthyroid Patient.
   ELIOT CORDAY, M.D., F.A.C.C., HENRY L. JAFFE, M.D., HERBERT GOLD, M.D., and JOHN H. WILLIAMS, M.D.
   Department of Medicine, Radiology and Radiation Therapy, Cedars of Lebanon Hospital and University of California School of Medicine, Los Angeles, Calif.

7. A Clinical Study of Internal Mammary Ligation for Angina Pectoris with Sham Operations.
   E. GREY DIMOND, M.D., F.A.C.C., C. F. KITTLE, M.D., J. E. CROCKETT, M.D., and L. M. RODRIGUEZ, M.D.
   Department of Medicine and Surgery, University of Kansas School of Medicine, Kansas City, Kan.

Fourth Scientific Session

Thursday, May 22, 1958, 1:30 to 3:30 P.M.

Symposium on
MYOCARDIAL METABOLISM

Moderator: RICHARD J. BING, M.D., F.A.C.C.
Professor of Medicine, Washington University School of Medicine, St. Louis, Mo.

1. Anerobic and Aerobic Metabolism.
   JOHN GERLEGY, M.D., PH.D.
   Established Investigator, American Heart Association; Associate Biochemist, Massachusetts General Hospital, Boston, Mass.

2. Effect of Heart Disease.
   RICHARD J. BING, M.D., F.A.C.C.
   Professor of Medicine, Washington University School of Medicine, St. Louis, Mo.

3. Effects of Cardiac Glycosides.
   GEORGE H. ACHESON, M.D.
   Professor of Pharmacology, University of Cincinnati College of Medicine, Cincinnati, Ohio.

4. Panel Discussion.

GROEDEL MEMORIAL LECTURE ON HUMANITIES IN MEDICINE

Thursday Evening, May 22, 1958

THE CHANGING PATTERNS OF DISEASE
PAUL A. CANNON, M.D.
Emeritus Professor of Pathology, University of Chicago Medical School, Chicago, Ill.

Fifth Scientific Session

Friday, May 23, 1958, 9:00 A.M. to Noon

Symposium on
SOME COMMON DRUGS USED IN THE TREATMENT OF HEART DISEASE

Moderator: JOHN H. MOYER, M.D., F.A.C.C.
Professor of Medicine, Hahnemann Medical School, Philadelphia, Penna.

1. Clinical Use of Cardiac Glycosides.
   E. GREY DIMOND, M.D., F.A.C.C.
   Professor and Chairman, Department of Medicine and Director of Cardiovascular Laboratory, University of Kansas Medical Center, Kansas City, Kan.

2. Clinical Use of Quinidine.
   REUBEN BERMAN, M.D., F.A.C.C.
   Associate Professor of Clinical Medicine, University of Minnesota School of Medicine, Minneapolis, Minn.

3. Diuretics.
   WALTER A. MODELL, M.D.
   Associate Professor of Pharmacology, Cornell University Medical College, New York, N. Y.

4. Monamine Oxidase Inhibitors.
   ALBERT SJOERDSMA, M.D.
   National Heart Institute, Bethesda, Md.

5. Hypotensive Agents.
   JOHN H. MOYER, M.D., F.A.C.C.
   Professor of Medicine, Head of Department of Medicine, Hahnemann Medical School, Philadelphia, Penna.

Sixth Scientific Session

Friday, May 23, 1958, 2 to 5:30 P.M.

Symposium on
SOME COMMON DRUGS USED IN THE TREATMENT OF HEART DISEASE (CONCLUSION)

6. Panel Discussion.

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CONVENTION GUEST LECTURE

4 to 5:30 P.M.

Chairman: GEORGE R. MENEELY, M.D., PRESIDENT OF THE COLLEGE

LONG TERM USE OF ANTICOAGULANTS
IRVING S. WRIGHT, M.D.
Professor of Clinical Medicine, Cornell University Medical College, New York, N. Y.

Discussion to be opened by
BENJAMIN MANCHESTER, M.D., F.A.C.C.
Washington, D. C.

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Seventh Scientific Session

Saturday, May 24, 1958, 9 A.M. to 12 Noon

Symposium on
MODERN MANAGEMENT OF TETRALOGY OF FALLOT

Moderator: J. MAXWELL CHAMBERLAIN, M.D., F.A.C.C.
Director of Thoracic Surgery, Roosevelt Hospital, New York, N. Y.

1. Selection of Patients and Time for Surgery.
   WILLIAM LIKOFF, M.D., F.A.C.C.
   Associate Professor of Medicine, Hahnemann Medical School, and Chief, Division of Cardiology, Bailey Thoracic Clinic, Philadelphia, Pa.

2. The Place of the Blalock Procedure.
   DWIGHT C. MCGOON, M.D.
   Division of Surgery, Mayo Clinic, Rochester, Minn.

3. The Status of the Potts Procedure.
   CLARENCE CRAFOORD, M.D.
   Professor of Thoracic Surgery, Karlinska Sjukhus, Stockholm, Sweden.

4. The Status of the Brock Procedure.
   SIR RUSSELL BROCK
   Chief Surgeon, Brompton Hospital, London, England.

5. The Definitive Operation—Open Heart Procedure.
   C. WALTON LILLEHEI, M.D., F.A.C.C.
   Professor of Surgery, University of Minnesota, Minneapolis, Minn.

6. Physiologic Changes Following Surgery for Tetralogy of Fallot.
   C. RAWLINS HANLON, M.D.
   Professor of Surgery and Director of Department of Surgery, St. Louis University School of Medicine, St. Louis, Mo.

7. Panel Discussion.

Eighth Scientific Session

Saturday, May 24, 1958, 1:30 to 5 P.M.

Symposium on

THE SURGICAL MANAGEMENT OF THE AORTIC VALVE

Moderator: IVAN BARONOFSKY, M.D.
Director of Surgery, Mount Sinai Hospital and Clinical Professor of Surgery, Columbia University, New York, N. Y.

1. Selection of Patients for Surgery.
   THOMAS H. BURFORD, M.D.
   Professor of Surgery, Washington University School of Medicine, St. Louis, Mo.

2. Aortic Valvulotomy (Transventricular).
   ROBERT P. GLOVER, M.D., F.A.C.C.
   Director, Cardiovascular Research Laboratory and Chief of Thoracic and Cardiac Surgery, Presbyterian Hospital, Philadelphia, Penna.

3. Aortic Valvulotomy (Transaortic).
   DWIGHT E. HARKEN, M.D., F.A.C.C.
   Associate Clinical Professor of Surgery, Harvard Medical School and Chief of Thoracic Surgery, Peter Bent Brigham and Mt. Auburn Hospitals, Boston, Mass.

4. Aortic Valvulotomy (Retrograde Coronary Sinus Perfusion).
   C. WALTON LILLEHEI, M.D., F.A.C.C.
   Professor of Surgery, University of Minnesota, Minneapolis, Minn.

5. Aortic Valvulotomy (Cardiac Arrest).
   DONALD B. EFFLER, M.D.
   Associate Professor of Thoracic Surgery, Frank E. Bunts Institute, Cleveland, Ohio.

6. Panel Discussion.
   Panel to be joined by F. JOHN LEWIS, M.D.
   Associate Professor of Surgery, Northwestern University Medical School, Chicago, Ill.

Committees for the Convention

SEYMOUR FISKE, M.D., F.A.C.C.
General Convention Chairman

SCIENTIFIC PROGRAM COMMITTEE

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EDWARD MASSIE, Chairman, Morris Alex, Malcolm B. Bawell, Richard J. Bing, Donald W. Bussman, Mary A. Davis, Julius Elson, James G. Janney, Sidney Jick, Chester Lynxwiler, J. F. Gerard Mudd, John J. Nuetzel, Charles Silverberg and Thomas J. Walsh.

SCHEDULE OF SOCIAL FUNCTIONS FOR THE LADIES

A special entertainment for the ladies will be provided during the convention of the American College of Cardiology in St. Louis, Missouri, May 21–24, 1958. Luncheons, a Fashion Show, and visits to historical and cultural centers have been arranged in the three-day program.

The cost is extremely modest, about $4.00 per day, per person. Please make advance reservations as early as possible to insure adequate preparations for all who wish to attend. For reservations please contact: Mrs. Julius Elson, Chairman, 5 Granada Way, La Due 24, Missouri.

Wednesday—May 21, 1958, 12 Noon–4:55 P.M.

Luncheon at Frontier Room of Montclair Apartments, 12 Noon.

Bus trip, 1 P.M., with visits to Jefferson Memorial, Museum of Fine Arts and the Zoo in Forest Park, and The Jewel Box, returning to Chase Hotel by 4:55 P.M.

The Frontier Room of the Montclair is noted for very fine food, especially Cantonese dishes. You will be served a Cantonese luncheon for $1.50 per person. The Montclair is just two short blocks from the Chase Hotel.

The Jefferson Memorial is located in Forest Park and was built during the time of the St. Louis Exposition. The Missouri Historical Society has taken it over and has many fascinating exhibits, including Indian relics and Missouri historical relics in the East wing of the building. The West wing houses the trophies and gifts received by Charles Lindbergh after his historic trans-Atlantic flight in 1927.

The Art Museum is located in beautiful Forest Park, top of Art Hill, and overlooks miles of the park. It is ranked as one of the four best in all of the United States. The museum's collection of Chinese bronze, ceramics, and paintings is world famous. A guided tour has been arranged.

St. Louis Zoo, 700 acres of park, features numerous unusual animals. A monkey show is scheduled.

The Jewel Box is aptly named as it does, indeed, look like a huge jewel box. Breathtakingly beautiful flowers are exhibited in the completely glass constructed showcase building. Soft organ music is played during the day.

Thursday—May 22, 1958, 10 A.M.–4:10 P.M.

Shaw's Garden is modeled after Kew Gardens and, many say, equally beautiful. There are 75 acres of trees and plants, more than 12,000 species. Winter flowering shrubs are in the Linnean House, only remaining greenhouse built in the lifetime of Henry Shaw who established the Garden in 1858. It is one of the few 19th century greenhouses in the country, has intricate fanlights and less glass than the more modern houses. Tropical lily ponds with pink, blue, and unusual hybrid water lilies, the world's rarest orchids, magnolias, palms, orange, and banana trees are shown there.

Grant's Farm was once owned and occupied by General U. S. Grant. Now owned by Anheuser-Busch it is the present home of August Busch. You will be taken on a tour of the farm and will see Mr. Busch's unusual collection of animals. The tour takes one and one-half hours and at the end of the tour refreshments will be served.

Friday—May 23, 1958, 10 A.M. –2:30 P.M.

Board buses at Chase hotel 10:00 A.M., visit to Campbell House followed by scenic ride along Mississippi River Front to see the Old Cathedral, Old Court House, and Eugene Field Home. A special luncheon and Fashion Show have been arranged at the Stix-Baer-Fuller Department Store. Afternoon will be free for shopping or bus may be taken back to Chase Hotel at 2:30 P.M.

The Campbell House is among the most historic buildings still standing in St. Louis. A narrow, three-story, gray painted brick building with stable summerhouse and wrought-iron fence, it is the last of the mansions that made Lucas Place the fashionable residential district in the ante-bellum period. Robert Campbell, an Irish fur trader, was a business leader of St. Louis for many years. The house was preserved intact and the furnishings are as they were when Mr. Campbell lived there. Everything is authentic, including the costumes of mid-Victorian period.

The Old Cathedral has been church property throughout the history of St. Louis. The first Mass was held there in 1764. The present building, fourth on the site, was completed in 1834.

The Old Court House is a Greek-revival building where much of the history of the Mississippi valley was written. The famous Dred Scott case had its beginning in one of the courtrooms and slaves were once auctioned from the steps on the east side.

The Eugene Field House, built about 1845, is a three-story red brick house where Eugene Field spent his boyhood.

Stix-Baer-Fuller is one of the country's leading department stores. A Fashion Show of new summer clothes will take place while luncheon is served there. Following luncheon, guests may see the exhibit of satellites in the Founder's Room or go shopping.